NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC., *et al.*, Plaintiffs, v. MYLAN LABORATORIES LTD., Defendant.	No. 20cv13103 (EP) (LDW) **OPINION** [redacted]

Padin, District Judge.

I. INTRODUCTION

This is a Hatch-Waxman Act case. Plaintiffs Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Pharmaceutica NV ("JPN"), and Janssen Research & Development, LLC ("JRD"), collectively "Janssen," manufacture Invega Trinza ("Trinza"), an FDA-approved, three-month long-acting injectable paliperidone palmitate (PP3M)[1] for treating schizophrenia and similar conditions. Defendant Mylan Laboratories Limited ("Mylan") seeks to use the Abbreviated New Drug Application ("ANDA") process to market a generic version of Trinza. Mylan's generic and its label are substantively identical to Trinza and Trinza's label.

But this case is not about the Trinza patent, which has expired. Janssen also has an active patent for a PP3M dosing regimen to reinitiate patients onto PP3M 4 to 9 months after a missed dose using a one-month long-acting injectable paliperidone palmitate (PP1M), then PP3M (the "693 Patent" or the "Patent"). Janssen asserts that Mylan's generic label, if the generic product comes to market, will inevitably induce health care providers ("HCPs") to infringe the 693 Patent's reinitiation regimen. And Mylan seeks to prove the 693 Patent's invalidity, arguing that the Patent's reinitiation dosing regimen, under various theories, should not (and/or never should have been) protected by patent law. Mylan's primary theory was obviousness, *i.e.*, that a person of ordinary skill in the art ("POSA") could have formulated the 693 Patent's claims using information publicly available before the Patent's issuance.

[1] Paliperidone Palmitate is abbreviated herein as "PP."

After a bench trial[2] and extensive post-trial briefing,[3] and having weighed the credible testimony and other evidence in the record, the Court finds that: (1) Janssen has demonstrated by a preponderance of the evidence that Mylan will inevitably induce HCPs to infringe the Patent's Asserted Claims (defined below); and (2) Mylan has not demonstrated by clear and convincing evidence that the 693 Patent is obvious or otherwise invalid.[4] The Court will therefore enter judgment against Mylan, and for Janssen, as to the 693 Patent.

[2] Trial was held on November 16 and 30 and December 1, 5, 6, 7, 8, and 9, 2022, and closing arguments on March 16, 2023. The Court acted as the trier of fact, adopting the standards utilized by a jury to evaluate credibility and weigh evidence. *See* Model Jury Charges of the Third Circuit, §§ 1.5, 1.6, and 1.7. The following witnesses testified for Janssen's infringement case: for Janssen, Roger Sommi, University of Missouri-Kansas City Professor of Pharmacy Practice; and for Mylan, Dr. Steven Berger, Board-Certified forensic and general psychiatrist. Next, for Mylan's primary invalidity case: for Mylan, Dr. Laird Forrest, University of Kansas Professor of Pharmaceutical Chemistry; and for Janssen, Jogarao Gobburu, University of Maryland Professor of Pharmacy Practice and Science; Steven Little, University of Pittsburgh Professor of Pharmaceutical Sciences, Immunology, and Bioengineering; and Dr. Sommi. And finally, regarding secondary considerations: for Mylan, Dr. Jeffery Stec, Berkeley Research Group Managing Director, and Drs. Berger and Forrest; and for Janssen, Dr. Christian Kohler, University of Pennsylvania School of Medicine Clinical Director of Neuropsychiatry; and Carla Mulhern, Managing Principal of Analysis Group.

[3] The Court extends its sincere appreciation to counsel for their professionalism, dedication, and collegiality during litigation and trial.

[4] This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

II. BACKGROUND

A. The Hatch-Waxman Act/ANDAs

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., the FDA must approve all new drugs before distribution in interstate commerce. 21 U.S.C. § 355(a). To secure new drug approval, an applicant may file a New Drug Application ("NDA") that includes the number and expiration date of any patents which claim the drug, or a method of using the drug, if an infringement claim could reasonably be asserted. *Id.* § 355(b)(2). "The FDA publishes the names of approved drugs and their associated patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations list a/k/a the 'Orange Book.'" *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010). An applicant seeking approval to market a generic version of an already-approved drug may file an Abbreviated NDA ("ANDA"), which "allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is 'bioequivalent' to the listed drug." *Id.* (citing 21 U.S.C. §§ 355(b)(2), 355(j)).

The Hatch-Waxman Act[5] aims to balance two competing policy interests: research and development of new drugs enabling competitors to bring low-cost generic copies of those drugs to market rapidly if those drugs are not entitled to patent protection. *See Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). To balance those interests, the Hatch-Waxman Act provides a means for pharmaceutical companies to resolve patent disputes relatively quickly. Ideally, it provides for a prompt determination of whether particular drugs made and sold

[5] The more common name for the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(c), 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066.

by brand-name pharmaceutical companies are protected by valid patents. If the patents are held to be infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held to be invalid or not infringed, the Act provides for prompt approval of the generic versions of the drugs by the FDA, which regulates the sale of pharmaceutical drugs in this country.

The Hatch-Waxman Act creates what is referred to as an "artificial" type of infringement that allows for the adjudication of the parties' rights in patents that would be infringed if the ANDA were issued and the generic product made, used, or sold. *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of patent infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of the ANDA's submission is to obtain approval to manufacture, use, or sell the patented drug. If a patent infringement suit is commenced within 45 days of a generic manufacturer notifying a brand-name manufacturer of the ANDA application, then the FDA may not approve the ANDA application until the expiration of a 30-month statutory period. *Id.* § 355(c)(3)(C).[6]

B. Parties, jurisdiction, and standing

Plaintiffs are JPI, JPN, and JRD (collectively "Janssen"). D.E. 99 (Final Pre-Trial Order ("FPTO")) 2 n.1, 6-8.[7] JPN owns the entire right, title, and interest in the 693 Patent and JPI holds New Drug Application ("NDA") No. 207946 for paliperidone palmitate three-month extended release injectable suspension ("PP3M") prescribed and sold under the Trinza trademark. FPTO 11, 14; PTX-2; PTX-3; PTX-4.

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[6] [redacted]

[7] Unless otherwise indicated, the Court cites to the FPTO's Stipulations of Fact contained in Section III. *See* FPTO 2, *et seq.*

Defendant Mylan Laboratories Limited ("Mylan") is a generic drug manufacturer who has filed Abbreviated New Drug Application ("ANDA") Nos. 212290, 215682, and 216228, seeking United States Food & Drug Administration ("FDA") approval to market a generic version of Janssen's Invega Trinza Product ("Mylan's Proposed ANDA Products"). FPTO 5, 33, 38, 43.

Because this action arises under United States patent laws, this Court exercises subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a); FPTO 1-2. JPN and JPI have standing to bring this suit. *Schwendimann v. Arkwright Advanced Coating, Inc.*, 959 F.3d 1065, 1072 (Fed. Cir. 2020).

C. Background for the invention

1. Schizophrenia and antipsychotic medications

Schizophrenia is a serious and disabling mental illness that affects about 1% of the population. Tr. 175:5-6 (Berger), 870:3-17 (Kohler). Schizophrenia is a type of psychosis, *i.e.*, a loss of contact with reality with positive symptoms (delusions, hallucinations) and negative symptoms (alogia, avolition) affecting the ability to manage day-to-day responsibilities, relationships, education, and employment. Tr. 54:9-55:6 (Sommi), 176:1-8 (Berger). Schizophrenia patients are often unemployed, poverty-stricken, homeless, and/or incarcerated. Tr. 58:14-17 (Sommi), 175:9-21 (Berger). The "largest mental health provider for schizophrenics" in the United States is the prison system. Tr. 902:16-19 (Kohler).

Schizophrenia has no cure. Tr. 56:21-22 (Sommi), 176:9-11 (Berger). Instead, practitioners aim for symptom improvement and relapse prevention through antipsychotic medications. Tr. 56:23-57:6, 58:1-13 (Sommi), 176:12-17 (Berger), 871:3-9 (Kohler). First-generation antipsychotics, like Thorazine (chlorpromazine), were introduced in the 1950s. Tr. 177:10-17 (Berger). They worked by targeting dopamine and came in the form of tablets, then

liquids, then short-acting injectables, then long-acting injectables. Tr. 59:16-61:20 (Sommi), 177:10-17 (Berger). Long-acting injectable antipsychotics ("LAIAs") have been available since at least the 1960s. Tr. 61:16-19 (Sommi).

Second-generation antipsychotics, which targeted serotonin, emerged in the 1980s with clozapine; like their first-generation predecessors, as pills, then liquids, then short-acting and long-acting injections. Tr. 177:18-23 (Berger). Though mitigating some first-generation side effects, the second-generation antipsychotics caused new, metabolic side effects like weight gain, increased risk of diabetes, and increased blood glucose. Tr. 60:23-61:9 (Sommi).

Continuous antipsychotic treatment avoids relapse; with each relapse, schizophrenia progresses to further loss of brain function and becomes harder to treat. Tr. 68:18-69:5 (Sommi), 871:9-21 (Kohler).

2. Medication nonadherence

Nonadherence accompanies the management of all chronic diseases, but is particularly prevalent and well-documented among schizophrenia patients. Tr. 67:4-9 (Sommi) (noting that 75% of patients over 18-month period stopped taking oral antipsychotics), 182:15-17 (Berger), Tr. 932:15-20 (Kohler), 1034:18-20 (Berger); PTX-97 at 15-16. Among the reasons for medication nonadherence are side effects associated with antipsychotics. Tr. 72:10-13 (Sommi), 911:1-3 (Kohler). Accordingly, clinicians seek to avoid those side effects. Tr. 873:1-11.

LAIAs, which reduce the "number of times the patient has to remember to take the medication," improve nonadherence. Tr. 1034:24-1035:6, (Berger), 873:19-21 (Kohler); Gopal Dep. Tr. 176:20-177:4; PTX-97 at 18. LAIAs enhance patient convenience, reduce relapses (which improves patient prognoses), and reduce caretaker burdens. Tr. 68:13-70:10 (Sommi). Moreover, because HCPs administer LAIAs, they can more accurately track medication adherence

and thereby assess patient response. Tr. 70:11-25 (Sommi). Nevertheless, despite LAIA benefits, HCPs—particularly "younger staff members"—are sometimes reluctant to prescribe them, in part because "many clinicians lack knowledge about practical issues, … including dose selection, pharmacokinetics, and what to do when a patient is late for an injection or has persistent symptoms after starting therapy." PTX-97 at 17.

3. Pharmacokinetics, Population Pharmacokinetics, and depot formulations

Pharmacokinetics is the practice of describing how a given drug will behave in a patient's body, *i.e.*, "what the body does to a drug" through absorption, distribution, metabolism, and excretion—how it enters, how it's processed, and how it leaves. Tr. 401:23-402:5 (Forrest), 806:23-807:28 (Gobburu). Monitoring pharmacokinetics requires obtaining drug levels by taking blood samples from patients and measuring drug levels at various points in time. Tr. 807:9-11 (Gobburu). Drug levels are then plotted on a plasma concentration time curve. Tr. 807:11-13 (Gobburu).

Depot drugs are drug formulations that last in a patient's body for different amounts of time. Tr. 400:22-401:5 (Forrest). An individual's response to a drug—including a depot drug—is unpredictable due to "genetics, disease, age, gender, body weight, drugs given concomitantly, and various behavioral and environmental factors." Tr. 807:5-19 (Gobburu); PTX-145[8] at 500. The response may also vary depending upon a drug's particle size. Tr. 400:25-401:5 (Forrest). Population pharmacokinetics ("pop-PK"), used in designing dosing regimens, accounts for these variations and allows scientists to "understand not only the average … but the spread of the data." Tr. 808:21-809:5 (Gobburu). To devise the claimed dosing regimens, the 693 Patent's inventors

[8] Rowland, Malcolm and Tozer, Thomas N., *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*, Fourth Edition (2011), Wolters Kluwer.

developed a "comprehensive [pop-PK] model" for PP and used that model to simulate various dosing regimen scenarios. PTX-1 at 17:25-46, 19:55-20:28, Figs. 4A-4C.

When a patient receives their first injection of a depot drug they have not previously been administered or are otherwise naïve to, they begin at zero concentration at zero time on a plasma curve. Tr. 402:18-25 (Forrest). For a typical injectable depot drug, a patient's plasma curve rises "very quickly." Tr. 403:11-19 (Forrest).

D. Trinza

Trinza, approved in May 2015, is a three-month long-acting injectable ("LAI") formulation of the second-generation antipsychotic PP. Tr. 73:22-25, 74:8-11 (Sommi). Invega Sustenna was the one-month, PP1M formulation. Tr. 74:1-3 (Sommi). When Trinza was launched, it was lauded as "revolutionary." PTX-226[9] at 5. It remains the only LAIA administered once every three months. Tr. 74:23-75:6 (Sommi).

When Trinza launched, HCPs had no experience with a three-month dosing regimen. Tr. 74:23-75:2 (Sommi), 874:22-875:1 (Kohler). HCPs had concerns about effectiveness and side effects; as to the latter, HCPs recognized that any side effects would have to be managed "over a much longer period of time." Tr. 875:1-24 (Kohler), Tr. 1058:15-16 (Berger) (acknowledging reluctance to prescribe Trinza: "We were questioning whether it would really last three months").

Trinza has been "very well received," has "fulfilled [HCP] expectations in providing effective treatment over a period of at least three months in people who were previously stabilized … [on] Invega Sustenna," and has demonstrated a "tolerable side effects profile." Tr. 876:2-9 (Kohler). Even Mylan's expert, Dr. Berger, hails it as a "wonderful drug." Tr. 243:23-24.

[9] Daghistani & Rey, *Invega Trinza*: *The First Four-Times-a-Year, Long-Acting Injectable Antipsychotic Agent*, P&T, Vol. 41, No. 4 (Apr. 2016).

E. The patent at issue: the 693 Patent

The 693 Patent "relates to a method for treating patients who have missed a treatment of 3-month paliperidone palmitate extended-release injectable suspension formulation." PTX-1 at 1:15-19, 17:16; Tr. 76:17-76:18 (Sommi). The Asserted Claims describe dosing regimens for administering PP to a patient that had been last administered PP3M 4 to 9 months ago. *See* PTX-1 at Claim 5.

1. Prosecution History

On April 5, 2016, Janssen filed the application that became the 693 Patent. FPTO 13. The application included Claims 1-8. DTX-8 at 40-42.

On November 1, 2017, the Patent Office Examiner ("Examiner") conducted prior art searches on the East and Google Scholar Databases. DTX-8 at 193. The Examiner's East search queries included "paliperidone," "three month," and the inventor names; the Examiner's Google Scholar search terms are not recorded. DTX-8 at 205-06.

On November 20, 2017, the Examiner rejected claims 1-8 as obvious over the 536 Publication in view of certain prior art, Osborne,[10] and on the ground of nonstatutory obviousness-type "double patenting" over claims 1-16 of U.S. Patent No. 9,439,906 (the "906 Patent"), which covers PP1M initiating (not re-initiation) dosing regimens. DTX-8 at 196-203. The Examiner did not reject the claims under 35 U.S.C. § 112, *i.e.*, lack of specification. *Id.*; Tr. 768:1-11 (Forrest).

In response to the double patenting rejection, Janssen argued that the 906 Patent concerned *PP1M's initial* dosing regimen, not the subject claims relating to a *missed PP3M* dosing regimen.

[10] Osborne et al., *Health-related quality of life advantage of long-acting injectable antipsychotic treatment for schizophrenia: a time trade-off study, Health and Quality of Life Outcomes* 10(35) (2012): 1-9; DTX-36.

DTX-8 at 217. In other words, a *missed PP3M* dosing regimen would not double-patent an *initial PP1M* dosing regimen. *Id.*

On June 14, 2018, the Examiner conducted updated searches on East and Google Scholar. *Id.* 236. Again, the East searches included "paliperidone," "three month," and the inventors' names. *Id.* 237. On June 27, 2018, the United States Patent and Trademark Office ("PTO") issued a Notice of Allowance, concluding that the 693 Patent's rejected claims are patentable. DTX-8 at 223. The PTO reasoned:

> While the closest prior art of 536 publication teaches a dosing regimen for a patient to get back onto PP1M after missed dose of PP1M, the prior art does not teach [PP3M] and exact numbers of reinitiation loading doses and maintenance doses and their amounts for patients who had been treated with a PP3M and had been last administered the PP3M more than 9 months or 4 to 9 months ago as claimed. No other prior art was found to teach that when a patient misses a dose of PP3M for extended period of time a patient must first be treated and stable on PP1M and then a PP3M injection is then given at the time that the patient would have received their next PP1M injection as claimed. Thus, the instant claims are novel and non-obvious over the prior art.

Id. 229.

The 693 Patent issued on December 4, 2018.

2. The Patent Specification

The 693 Patent's specification explains that PP3M "offers the prospect of fewer opportunities for nonadherence than currently available [LAI] formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentration and its associated negative consequences in patents with schizophrenia." PTX-1 at 2:15-19. In other words, PP3M works because there are fewer chances for the drug to wear off because of a missed dose.

But missed doses still happen. *Id.* 2:20-22. "Consequently, there is a need to reinitiate a dosing regimen for patients who miss their regularly scheduled dose of medication." *Id.* 2:22-24.

"Thus, the objective of the present application is to provide a dosing regimen of [PP] for patients in need of a treatment who have missed their 3 month (±2 weeks) dose of [PP3M]." *Id.* 2:24-29.

The specification summarizes the claimed dosing regimens. *Id.* 2:32-3:56. It describes a "dosing regimen for administering an injectable [PP] depot to a patient in need of psychiatric treatment that has been treated with" PP3M, "wherein said patient misses for a period of between about four months and about nine months" the "next scheduled maintenance dose" of PP3M. *Id.* 2:32-42. The claimed dosing regimens "compris[e]" three numbered doses of PP1M or PP3M corresponding to the Asserted Claims.

The specification also provides detailed information about PP1M and PP3M formulations for use in the dosing regimens, including:

- Composition for the 1-month and 3-month formulations: the active ingredient (PP), the types of inactive ingredients, the concentrations of the ingredients. PTX-1 at 13:49-56, 13:62-14:3.
- Average and preferred particle size ranges for PP1M and PP3M. *Id.* 9:39-51.
- PP1M and PP3M manufacturing instructions. *Id.* 11:23-29, 11:50-12:35.
- Examples of PP1M and PP3M formulations that disclose specific inactive ingredients. *Id.* 4:33-39, 13:56-62.
- Description of Sustenna and Trinza as commercial embodiments of PP1M and PP3M, respectively. *Id.* 4:18-20, 5:23-25, 5:44-46, 6:63-65.

F. The Asserted Claims

The 693 Patent's Asserted Claims include independent claim 5 and dependent claims 6-7 and 9-14. All dependent claims depend directly or indirectly from claim 5. *See* PTX-1 at 21:10-22:3. As goes claim 5, so go the rest.

Claim 5 claims a PP3M reinitiation dosing regimen for a patient who had their last dose 4 to 9 months prior:

> A dosing regimen for administering an injectable paliperidone depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M

injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:

(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
(2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
(3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

Claims 6-7 depend directly from claim 5 and narrow this method to a specific patient in need of treatment for psychosis (claim 6) and schizophrenia (claim 7). *Id.* 21:40-43.

Claim 9 depends directly from claim 5 and narrows this method to a specific time for administering the second PP1M reinitiation dose to "about 7 days" after the first PP1M reinitiation loading dose. *Id.* 24:49-51.

Claim 11 depends directly from claim 5 and narrows this method to a specific time for the administering of the PP3M reinitiation dose to "about 30 days" after the second PP1M reinitiation loading dose. *Id.* 21:52-54. Claim 12 depends from claim 11 and narrows this method to a specific time for administering the PP3M reinitiation dose to "30 days" after the second PP1M reinitiation loading dose. *Id.* 21:55-57.

Claim 13 depends directly from claim 5 and narrows this method to a specific time for administering the PP3M reinitiation dose to "about a month" after the second PP1M reinitiation loading dose. *Id.* 21:58-60. Claim 14 depends from claim 11 and narrows the method to a specific time for administering the PP3M reinitiation dose to "a month" after the second PP1M reinitiation loading dose. *Id.* 22:1-3.

The 693 Patent covers Trinza. FPTO 4. In turn, Trinza's label dosing instructions track the 693 Patent's Asserted Claims. Specifically, Trinza's label instructs HCPs not to administer the next Trinza dose if a patient missed a dose between 4 and 9 months prior, but to use the reinitiation regimen shown in the table above. PTX-43 at 5. That table tracks the Asserted Claims. Tr. 88:14-92:8 (Sommi), Tr. 244:14 (Berger).

G. Mylan's Proposed Labels

Mylan filed ANDA Nos. 216228, 212290, and 215682 seeking FDA approval to market and sell Mylan's Proposed ANDA Products in 273, 410, 546, and 819 mg PP dose strengths. FPTO 33, 38, 43. The proposed labels ("Mylan's Proposed Labels") are substantially identical to the Trinza label. PTX-92 (216228); PTX-162 (212290); PTX-133 (215682). Other than replacing the Trinza and Sustenna brand names with generic names, the Proposed ANDA Products include the same text in the "Missed Doses" section. FPTO 25.

Mylan's Proposed Labels state: "To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)." PTX-92, PTX-133, PTX -162 at 1; PTX-595 at 5. Section 2 of Mylan's Proposed Labels is entitled "Dosage and Administration." PTX-92, PTX-133, PTX-162 at 4; PTX-595 at 9. And Section 2.3 is entitled "Missed Doses." PTX-92, PTX-133, PTX-162 at 6; PTX-595 at 14. Table 2 of the Proposed Labels' missed dosing regimen reproduces (except for the Sustenna name) Claim 5's PP3M reinitiation regimen using PP1M:

Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid[a] or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

[a] See Instructions for Use for deltoid injection needle selection based on body weight.

PTX-92, PTX-133, PTX-162 at 7; PTX-595 at 15. On November 15, 2022, Mylan produced to Janssen an updated proposed label that Mylan had submitted to the FDA. PTX-595; Tr. 103:19-21.[11]

III. ANALYSIS

A. INFRINGEMENT: Janssen established that Mylan's Proposed Labels will induce HCPs to infringe upon the Asserted Claims

It is "an act of [patent] infringement to submit" an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2); *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990). In ANDA cases, the infringement analysis "is focused on a comparison of the asserted patent [claims] against the product that is likely to be sold following ANDA approval." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018) (cleaned up).

Janssen contends that Mylan, a generic manufacturer, will induce infringement of the Asserted Claims rather than directly practice them. "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To establish induced infringement, a plaintiff must prove (1) direct infringement and (2) that the defendant had the specific intent to

[11] Any changes to Mylan's Proposed Labels did not impact the infringement analysis.

induce infringement. *Vanda*, 887 F.3d at 1129. A patentee must prove infringement by a preponderance of the evidence. *Id.* at 1125.

For the reasons detailed below, Janssen has demonstrated by a preponderance of the evidence that Mylan will induce infringement of the Asserted Claims. Specifically, Janssen presented evidence that: (1) Mylan's Proposed Labels expressly instruct HCPs to infringe the Asserted Claims for patients who last received PP3M 4 to 9 months ago for reinitiation onto PP3M; (2) some patients will inevitably be reinitiated on PP3M between 4 and 9 months after their last dose; and (3) this will inevitably lead some HCPs to practice the patented dosing regimens of the Asserted Claims.

Conversely, the Court is unpersuaded by Mylan's counterargument—that there is no infringement under a "divided infringement" theory and that many patients will not be treated according to the Asserted Claims. Mylan contends, in substance, that Mylan cannot induce direct infringement because the steps of the claimed dosing regimens will be carried out by two independent actors, neither of which is Mylan: the patient, who missed a dose of PP3M and chose to return for treatment three times, and that patient's HCP, who would administer the claimed dosing regimen. Tr. 172:24-173:7 (Berger). For the reasons below, this theory lacks any legal or factual basis.

1. Mylan's Proposed Labels essentially duplicate Janssen's and recite each limitation of the Asserted Claims

In deciding induced infringement, "courts compare[] the wording of the label to the patent claims." *BTG Int'l Ltd. v. Amneal Pharms. LLC*, 352 F. Supp. 3d 352, 394 (D.N.J. 2018), *appeal dismissed in relevant part as moot*, 923 F.3d 1063, 1077 (Fed. Cir. 2019). Proposed drug labels "encompass infringement" if the "label meets the claim limitations of the patent" or the "label language aligns with the language" of patent claims. *Id.* at 394-95; *see also GlaxoSmithKline LLC*

v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1330 (Fed. Cir. 2021) (affirming induced infringement where expert "marched through [the] label explaining how it met the limitations of [the] claim"), *reh'g and reh'g en banc denied*, 25 F.4th 949 (Fed. Cir. 2022), *petition for cert. pending*, No. 22-37 (filed July 11, 2022). Here, Dr. Sommi credibly demonstrated that the missed dose instructions in Mylan's Proposed Labels induce infringement of each element of the Asserted Claims.

a. Claim 5

Claim 5 claims a dosing regimen. PTX-1 at 21:10-11 ("A dosing regimen for administering an injectable [PP] depot … ."); Tr. 79:25-80:3, 97:17-21, 116:1-2 (Sommi); Tr. 285:7-9 (Berger). Mylan's Proposed Labels likewise set forth a "reinitiation" dosing regimen. PTX-92 at 4, 6-7 ("2 DOSAGE AND ADMINISTRATION"; "2.3 Missed Doses . . . Table 2. Re-initiation Regimen . . . ."); PTX-133 at 4, 6-7; PTX-162 at 4, 6-7; PTX-595 at 9, 14-15; Tr. 97:17-25 (Sommi).

Next, Claim 5 also identifies a patient in need of treatment for psychosis, schizophrenia, or bipolar disorder. PTX-1 at 21:11-12; Tr. 78:10-12, 97:19-98:3 (Sommi). Mylan's Proposed Labels also identify a patient in need of treatment for schizophrenia. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; PTX-595 at 9; Tr. 97:19-98:3 (Sommi).

Claim 5 also identifies a patient who has been treated with PP3M and had been last administered PP3M four to nine months ago. PTX-1 at 21:11-14 ("to a patient … that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient"); Tr. 78:10-12, 82:2-8, 125:19-22 (Sommi), 240:25-241:3 (Berger). Again, Mylan's Proposed Labels also identify a patient treated with PP3M last administered a dose of PP3M four to nine months ago. PTX-92 at 6-7; PTX-133 at 6-7; PTX-162 at 6-7; PTX-595 at 14-15; Tr. 97:25-98:3, 106:2-15 (Sommi).

Next, Claim 5 identifies the first step of the claimed dosing regimen as "(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M." PTX-1 at 21:17-18; Tr. 98:4-6, 123:9-12 (Sommi). And Mylan's Proposed Labels likewise identify the first reinitiation regimen step as "[a]dminister[ing] 1-month [PP] extended-release injectable suspension . . . (into deltoid muscle) [on] Day 1 [of the re-initiation regimen]." PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:4-8 (Sommi).

Next, Claim 5 identifies the second step of the claimed dosing regimen as "(2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose." PTX-1 at 21:19-22; Tr. 98:6-9 (Sommi). Mylan's Proposed Labels likewise identify the second reinitiation regimen step as "[a]dminister[ing] 1-month [PP] extended-release injectable suspension . . . (into deltoid muscle) [on] Day 8 [of the reinitiation regimen]" or seven days after the first reinitiation loading dose of 1-month PP extended-release injectable suspension. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:6-9 (Sommi).

Likewise for the third reinitiation regimen step, which Claim 5 identifies as "(3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M." PTX-1 at 21:23-26; Tr. 98:10-13, 124:21-23 (Sommi). Mylan's Proposed Labels also identify the third dosing regimen step as "administer[ing] 3-month [PP] extended release injectable suspension (into deltoid or gluteal muscle) [on] "1 month after Day 8 [of the dosing regimen]" or "1 month" after the second reinitiation dose of PP1M. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13 (Sommi).

Claim 5's table lists the PP1M and PP3M reinitiation dose amounts:

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

PTX-1 at 21:31-39; Tr. 98:14-17, 127:3-22 (Sommi). The reinitiation dose amounts are based on the amount of the missed dose of PP3M. PTX-1 at 21:27-29 ("wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose"); Tr. 78:24-79:4 (Sommi). Table 2 of Mylan's Proposed Labels does the same:

Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid[a] or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

[a] See Instructions for Use for deltoid injection needle selection based on body weight.

PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:14-17 (Sommi). The dose amounts of the reinitiation doses are similarly based on the amount of the last dose of PP3M and track the amounts in claim 5. PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:14-17 (Sommi) ("[Y]ou can see that the milligram equivalents in the Claim 5 are exactly the same as the milligrams of the PP1M and PP3M products.").

b. Claims 6 and 7

Claim 6 is "[t]he method of claim 5, wherein said patient is in need of treatment for psychosis." PTX-1 at 21:40-41; Tr. 100:13-25 (Sommi). Patients with schizophrenia have psychosis and will therefore be in need of treatment for psychosis. Tr. 100:18-25 (Sommi), 176:8 (Berger) ("Schizophrenia is a type of psychosis."). Accordingly, Mylan's Proposed Labels also identify a patient in need of treatment for psychosis. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; Tr. 97:17-98:3, 100:18-101:6 (Sommi).

Similarly, Claim 7 is "[t]he method of claim 5, wherein said patient is in need of treatment for schizophrenia." PTX-1 at 21:42-43; Tr. 100:16-101:6 (Sommi). Mylan's Proposed Labels also identify a patient in need of treatment for schizophrenia. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; Tr. 97:17-98:3, 100:18-101:6 (Sommi).

c. Claim 10

Claim 10 is "[t]he method of claim 9, wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M." PTX-1 at 21:49-51. Claim 10 specifies that the second step of the claimed dosing regimen is seven days after the first reinitiation loading dose. Tr. 101:7-14 (Sommi). Mylan's Proposed Labels identify the second administering step of the re-initiation dosing regimen as "[a]dminister[ing] [PP1M] . . . (into deltoid muscle) [on] Day 8 [of the re-initiation regimen]," or seven days after Day 1's first PP1M reinitiation loading dose. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 101:10-23 (Sommi).

d. Claims 11 and 14

Claim 11 is "[t]he method of claim 5, wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M." PTX-1 at 21:52-

54. Claim 11 specifies that the claimed dosing regimen's third step is about 30 days after the second PP1M reinitiation loading dose. Tr. 102:3-13 (Sommi). Mylan's Proposed Labels also identify the third administering step of the reinitiation dosing regimen as "administer[ing] [PP3M (into deltoid or gluteal muscle)" on "1 month after Day 8 [of the re-initiation dosing regimen]" or "1 month" after the second PP1M re-initiation dose on Day 8. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13, 101:24-102:22 (Sommi).

And finally, Claim 14 specifies that the third step of the claimed dosing regimen is about a month after the second PP1M reinitiation loading dose: "[t]he method of claim 11[,] wherein the reinitiation dose of PP3M is administered a month after administering said second [PP1M] reinitiation loading dose." PTX-1 at 22:1-3; Tr. 102:4-13 (Sommi). As with the other claims, Mylan's Proposed Labels also identify the third administering step of the reinitiation dosing regimen as "administer[ing] [PP3M] (into deltoid or gluteal muscle) [on] "1 month after Day 8 [of the re-initiation dosing regimen]" or "1 month" after the second PP1M re-initiation dose. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13, 101:24-102:22 (Sommi).

2. Mylan's divided infringement defense

Janssen alleges, in substance, that Mylan's proposed Trinza generic will inevitably induce HCPs—those administering the drug to patients—to infringe upon the claimed dosing regimens. Inherent in Hatch-Waxman/ANDA litigation is an element of copying; generic drug manufacturers will often simply stipulate to infringement. 21 U.S.C. § 355(j); *Novartis Pharm. Corp. v. Teva Pharm. USA, Inc.*, No. 05-CV-1887 (DMC), 2009 U.S. Dist. LEXIS 103104, at *56 (D.N.J. Nov. 5, 2009). This makes logical sense; the FDA requires a generic to be bioequivalent (chemically the same) as the patented substance, with an identical label. Tr. 222:6-20 (Berger).

Here, Mylan contends that there will be no *direct* infringement because the Asserted Claims' reinitiation dosing regimen will be carried out by two independent actors: the patient, who missed a dose of PP3M and chose to return for treatment three times, and that patient's HCP, who administers the claimed dosing regimen. Tr. 172:24-173:7 (Berger). This is the "divided infringement issue." Tr. 204:7-10 (Berger).

Mylan's divided infringement theory posits "seven steps" split between the patient and the HCP:

> 41. Accordingly, the steps of the claimed method include four (4) steps where the patient is independently responsible and three (3) steps where the healthcare professional is responsible. Accordingly, the steps and party responsible for practicing the steps are as follows:
>
> **1. miss a dose (patient);**
> **2. return for treatment between 4 to 9 months since last injection (patient);**
> 3. administering intramuscularly first reinitiation dose of PP1M[30] (healthcare professional);
> **4. return for treatment on about the 4th day to about the 12th day after first reinitiation loading dose (patient);**
> 5. administering intramuscularly a second reinitiation loading dose of PP1M (healthcare professional);
> **6. return for treatment on about the 23rd day to about the 37th day after second reinitiation loading dose of PP1M (patient); and**
> 7. administering intramuscularly a reinitiation dose of PP3M (healthcare professional).

FPTO, Mylan Contested Facts ¶ 41; Tr. 186:10-188:19; 287:15-20 (Berger).

In contrast, Janssen's infringement theory asserts that the Asserted Claims comprise three steps of administering the three reinitiation doses, numbered as "(1)," "(2)," and "(3)" in the claims. Tr. 79:5-86:25 (Sommi).

> (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
> (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
> (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

a. Mylan's divided infringement defense fails because it was untimely

Local Patent Rule 3.6 sets forth disclosure requirements for Hatch-Waxman Act/ANDA matters, including the disclosure of "Non-Infringement Contentions and Responses" from a "party opposing an assertion of patent infringement." L. Pat. R. 3.2A, 3.6(g). "Local Patent Rules exist to further the goal of full and timely discovery and provide all parties with adequate notice and information with which to litigate their cases," as well as to "require parties to crystallize their theories of the case early in the litigation and to adhere to those theories once they have been disclosed." *Celgene Corp. v. Hetero Labs Ltd.,* No. 17-3387, 2021 U.S. Dist. LEXIS 159262, at *12 (D.N.J. Mar. 29, 2021) (cleaned up).

Here, Mylan's divided infringement theory was not disclosed in its contentions, and appeared improperly for the first time in Mylan's rebuttal expert report. *See*, *e.g.*, *Chiesi United States v. Aurobindo Pharma United States*, No. 19-18756, 2022 U.S. Dist. LEXIS 20102, at *15-16 (D.N.J. Jan. 9, 2022) (granting motion in limine precluding testimony on indefiniteness theory that was not disclosed in contentions); *Celgene*, 2021 U.S. Dist. LEXIS 159262, at *59 (D.N.J. Mar. 29, 2021) (striking invalidity theory not raised in contentions because it is "impermissible" to introduce new theories in an expert report without amendment); *Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, No. 12-3289 (PGS)(LHG), 2014 U.S. Dist. LEXIS 37002, at *23 (D.N.J. Jan. 6, 2014) (striking portions of expert reports that rely on prior art not disclosed in contentions).

Janssen argued in pre-trial motions that Mylan did not raise this defense, to Janssen's detriment, until too late in the litigation. Indeed, Mylan's May 26, 2021 Non-Infringement Contentions, presented two theories, neither of which alleged divided infringement. First, Mylan asserted that its Proposed Labels would not directly infringe the reinitiation dosing regimen because Mylan itself does not administer the claimed dosing regimen to the patient; and second,

that Mylan would not have any control over whether patients are treated with the dosing regimen. D.E. 81-3.

Neither of these theories plausibly assert the "seven steps" divided infringement theory that Mylan actually pursued at trial, despite Mylan's best efforts—*in limine* and now after trial—to shoehorn the theory into its Non-Infringement Contentions. The contentions do not contain the words "divided infringement," cite no case law on divided infringement, and do not assert that the Asserted Claims have seven steps. *See id.* Rather, the contentions alleged that "*Mylan* will not directly or indirectly infringe the Asserted Claims" because "*Mylan* does not perform the requisite administering step. … *Mylan* does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that *Mylan*, itself, does not practice, *i.e.*, treating a subject having a disorder." *Id.* at 4 (emphases added).

Mylan, in other words, was arguing that *Mylan* did not infringe or induce infringement, not—as at trial—that *patients* acted in concert with HCPs to infringe. Even the most expansive reading of Mylan's Non-Infringement Contentions would not reveal any divided infringement defense. Mylan never sought to amend its Non-Infringement Contentions to add a divided infringement defense; the first mention appeared in Dr. Berger's expert report. *See* D.E. 72-12. It was therefore untimely. Nevertheless, for the reasons below, it is also unpersuasive on its merits.

b. Even if the divided infringement defense had been timely, the Court agrees with Janssen that a single entity (a healthcare provider) performs the claimed reinitiation dosing regimen's three steps

The parties dispute whether a patient's role constitutes a "descriptor of the clinical situation" (Janssen) or a claimed step (Mylan). As detailed below, the Asserted Claims' plain language favors Janssen's interpretation. The Asserted Claims steps are carried out by a single actor: an HCP.

The heart of the infringement dispute here is whether Mylan's Proposed Labels will induce *direct* infringement. Whether the infringement is direct depends on whether any claimed dosing regimen steps will be performed by a second actor—like, according to Mylan, the patient missing a dose and returning for treatment three times. If the HCP is the only actor, Mylan's Proposed Labels will induce infringement by the HCP. If the HCP and the patient are dual actors each performing different claimed steps, there will not be infringement.

Direct infringement "occurs where all steps of a claimed method are performed by or attributable to a single entity." *Akamai Techs., Inc. v. Limelight Networks*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (*en banc*). "Divided infringement" refers to the situation where "no single actor performs all steps of a method claim." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017). When the steps of the method are divided among multiple actors, the claimed method is infringed only if "the acts of one are attributable to the other such that a single entity is responsible for the infringement." *Id.*

Method-of-treatment claims sometimes have requirements that are not themselves steps of a claimed method. *See, e.g.*, *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 576 (D. Del. 2018) ("mild or moderate hepatic impairment" not a claimed step), *aff'd sub nom.*, *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019); *see also* Tr. 28:12-22, 33:9-17 (Mylan's counsel acknowledges that "passive" diagnoses like cancer or schizophrenia are not claimed steps).

The infringement analysis here turns on whether a patient's missed dose or choice to return for the claimed reinitiation regimen are "steps" of the Asserted Claims. Janssen limits its interpretation to the plain language of the Asserted Claims: three reinitiation injections by the HCP, three steps by one actor. Mylan interprets additional steps: the patient missing a dose and returning

three times for the injections (four steps), plus the injections (three more steps, for a total of seven). The Court agrees with Janssen: the injections comprise the only three claimed steps, and an HCP administers each step. Accordingly, Mylan's Proposed Labels will induce direct infringement by a single actor.

Determining the number of steps in a claimed method is a question of "claim construction." *In re Biogen '755 Patent Litig.*, No. 10cv2734, 2016 U.S. Dist. LEXIS 42608, at *7 (D.N.J. Mar. 28, 2016). "A claim construction analysis must begin and remain centered on the claim language itself." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "When claim language has as plain a meaning on an issue, … leaving no genuine uncertainties on interpretive questions relevant to the case, it is particularly difficult to conclude that the specification reasonably supports a different meaning." *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1360 (Fed. Cir. 2015).

The Asserted Claims "compris[e]" three steps: "administering" the three "reinitiation" doses that are enumerated (1), (2), and (3) in claim 5 to a schizophrenia patient had had their last injection four to nine months prior. PTX-1 at 21:17-29 ("(1) administering . . . ; (2) administering . . . ; (3) administering . . . ."); Tr. 79:5-80:3; 98:4-17, 115:25-116:2, 125:19-22 (Sommi). The dispute centers on the significance of the requirement that a schizophrenia patient miss a dose and return for another four to nine months after the missed dose. Janssen calls this a "descriptor of the clinical situation" in which the claimed dosing regimens are to be administered—not a claimed step. Tr. 82:1-8 ("It just helps me understand who the patient is that I'm treating."), 85:10-18, 86:13-18 ("These are instructions for the [HCP]. These are not instructions to patients. … These are not drugs that are administered by anybody other than a[n HCP]."), 125:19-22 (Sommi).

But the meaning here is plain: patients arriving *having missed* a dose, and HCPs *administer* three reinitiation doses. The three administrations are the three claimed steps. *See Core Wireless Licensing S.A.R.L. v. Apple Inc.*, No. 15-cv-05008, 2016 U.S. Dist. LEXIS 150795, at *14 (N.D. Cal. Oct. 31, 2016) (distinguishing the claimed steps, which "each start on a separate line with a gerund . . . demonstrating how the method should be performed," *e.g.*, storing, inserting, and sending, from other claim limitations, which "describe the environment in which the method . . . is practiced," *e.g.*, "the radio network controller configured to select"); *Amag Pharm., Inc. v. Sandoz, Inc.*, No. 16-cv-1508, 2017 U.S. Dist. LEXIS 112172, at *71 (D.N.J. July 19, 2017) ("It is important to remember that the elements, or the body, of a method claim are method steps, which should usually be verbal (gerundial) phrase, introduced by a gerund or verbal noun (the '-ing' form of a verb).").

It is true, as Mylan argues, that "doses do not miss themselves." Mylan Resp. Br. 7. But that does not mean, however, that missing a dose is a claimed step. Although having "been last administered a PP3M injection 4 to 9 months ago" is a requirement of the Asserted Claims, it is not a step of the claimed dosing regimens. *See, e.g., Orexigen Therapeutics, Inc. v. Actavis Lab'ys, FL, Inc.*, 282 F. Supp. 3d 793, 798 (D. Del. 2017) (holding that the act of diagnosing obesity is not a step of a claimed method of treating obesity "comprising administering [a pair of compounds] to an individual who has been diagnosed as suffering from overweight or obesity");[12] *In re Biogen '755 Patent*, 2016 U.S. Dist. LEXIS 42608, at *4-8 ("produced by" and "transformed by" were

[12] *Orexigen* rejected a mirror image of Mylan's divided infringement argument: that the doctor's initial diagnosis of a patient's obesity was the first claimed step before the patient administered the drug. But a "plain reading of this claim limitation indicates that the individual will already be diagnosed prior to the method being performed." *Orexigen*, 282 F. Supp. 3d at 812. In other words, the claimed treatment's prerequisite (*Orexigen*'s obesity diagnosis and a missed treatment here) has already occurred.

not steps of claimed method because they conveyed action that "'must have been' done rather than what 'must be' done). Mylan's contention that a patient's missed dose or choice to return for treatment can be (or are here) claimed steps lacks any precedential or factual support. To the contrary, there is ample reason to conclude that missing a dose and returning are merely preconditions to administration.

The Asserted Claims' plain language supports this interpretation in a different way. The dosing regimen is administered "to a patient" who meets certain criteria, including having "been last administered a PP3M injection 4 to 9 months ago." PTX-1 at 21:10-16; Tr. 84:22-85:2 (Sommi). The use of past-tense language makes clear that the patient missed a dose and returned for treatment *before* the claimed dosing regimens are administered. PTX-1 at 21:13-15 ("wherein said patient had been last administered a PP3M injection 4 to 9 months ago").

Moreover, the Court cannot agree with Dr. Berger that the tenses used in the Asserted Claims were "irrelevant." Tr. 286:13-17 (Berger). Elsewhere, he asserted that the passage stating, "wherein said patient had last been administered PP3M four to nine months ago" was the "present tense." Tr. 286:20-24 (Berger). On cross-examination, however, Dr. Berger conceded that the claim language recites only three steps "in writing," but stated that the claim language "is not correct" because there are actually "seven steps." Tr. 290:1-2, 287:19-20, 297:2-11 ("[F]or any treatment that[i]s administered by a health care professional at a health care facility," patients "have to show up."). Dr. Berger took this example to its logical extreme; asked about medications for overdose treatment, he would consider "the patient overdosing to be the first step in a dosing regimen for a drug indicated to treat overdose[.]" Tr. 297:12-19. Or in a baking context, the step preceding mixing eggs with milk would require getting a bowl from the cupboard. Tr. 300:13-19. The theoretical *other* steps might be infinite.

Nor can the Court agree, as Mylan urges, that the Asserted Claims' prosecution history supports Mylan's divided infringement theory. Mylan points specifically to Janssen's statement in the prosecution history that the Asserted Claims "are solely directed to what patients should do if a dose of PP3M is missed and they desire getting back on the medication." DTX-8 at 217, 0216; *see also* Mylan Resp. Br. 11. This describes what patients should do in the situation where the patient has missed a dose of PP3M—how they arrive at the point where claimed steps (the HCP's administration) begin, not any active role that patients play in the administration.

Whatever steps Mylan attempts to inject into the Asserted Claims, there are only three claimed "*administering*" steps, and therefore only one administering actor: the HCP. Tr. 96:23-97:7, 139:3-7, 146:10-15 (Sommi); Tr. 291:5-8 (Berger); PTX-92 at 4 (§2.1: "[e]ach injection must be administered only by a healthcare professional."); PTX-133 at 4; PTX-162 at 4; PTX-595 at 6; Tr. 139:3-7 (Sommi). With only one actor, there is no divided infringement. Next, the Court turns to whether Mylan specifically intends to induce infringement.

3. Mylan specifically intended to induce infringement

In ANDA cases, induced infringement requires showing that the proposed labels "encourage, recommend, or promote infringement." *Vanda*, 887 F.3d at 1129. Proposed labels induce infringement if they either "implicitly or explicitly encourage or instruct users to take action that would inevitably lead to" infringement. *See GlaxoSmithKline*, 7 F.4th at 1330. Here, Janssen proved inducement by presenting evidence that Mylan's Proposed Labels explicitly instruct HCPs to practice the Asserted Claims, and inevitably lead HCPs to infringe the Asserted Claims.

a. The explicit instructions in Mylan's Proposed Labels establish specific intent

Whether the Court infers specific intent "depends on how explicitly the instructions suggest the infringement, any direct evidence, the Court's fact-finding conclusions and the surrounding

circumstances." *Acorda Therapeutics Inc. v. Apotex Inc.*, Civil Action No. 07-4937, 2011 U.S. Dist. LEXIS 102875, at *47 (D.N.J. Sep. 6, 2011), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012). "Depending on the clarity of the instructions, the decision to continue seeking FDA approval of those instructions may be sufficient evidence of specific intent to induce infringement." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017). "Proposed labeling that instructs [an] infringing use[] is generally sufficient to support a finding of intentional inducement." *BTG*, 352 F. Supp. 3d at 399 (collecting cases).

Mylan's Proposed Labels explicitly instruct HCPs to reinitiate patients onto PP3M in an infringing manner, by directing HCPs "[t]o manage missed doses." Mylan's Proposed Labels explicitly instruct HCPs to practice the Asserted Claims by directing HCPs to Section 2.3 "[t]o manage missed doses." PTX-92 at 1; PTX-133 at 1; PTX-162 at 1; PTX-595 at 5; Tr. 120:5-9 (Sommi); Tr. 260:4-9 (Berger). Under Section 2.3's subheading, "Missed Dose 4 Months to 9 Months Since Last Injection," Mylan's Proposed Labels instruct HCPs that, where the patient last received a PP3M dose four to nine months ago, "do NOT administer the next dose of [PP3M]. Instead use the re-initiation regimen in Table 2." PTX-92 at 6-7; PTX-133 at 6-7; PTX-162 at 6-7; PTX-595 at 14-15. And Table 2, in turn, directs HCPS to perform all three administrating steps of the claimed re-initiation regimen. PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15.

Moreover, missed doses and patients returning between 4 and 9 months after a missed dose are inevitable, meaning that infringement of the claimed reinitiation regimen would be inevitable. Even Mylan's expert, Dr. Berger, testified that Trinza/PP3M did not solve nonadherence among schizophrenia patients. Tr. 182:21-22 (Berger) ("No. It's still a problem, still a big problem."); Tr. 77:9-11, 107:25-108:1 ("So if this were a perfect world, then you wouldn't have to have a missed dose section."), Tr. 119:13-16 (Sommi); Tr. 873:13-874:1, 884:6-7 (Kohler)

("[N]onadherence will occur again."); *see also* PTX-1 at 2:20-24 ("Even with a drug administered once every 3 months . . . , patients at times miss their doses of medication."). Dr. Berger acknowledged that "more than 50 percent" of Trinza patients have missed a dose, including "20 to 30 percent" returning for an appointment 16 or more weeks (about 4 months) after the missed dose. Tr. 251:1-14, 262:4-8, 310:12-18 (Berger).[13]

Dr. Kohler likewise testified that he had multiple patients who returned for a reinitiation dose of Trinza between 4 and 9 months after their last dose. Tr. 886:11-14, 888:18-24, 890:1-6 (Kohler).[14] Thus, even though the Trinza label advises that missed doses should be avoided, many patients still miss their PP3M doses, and inevitably return within 4 to 9 months for reinitiation.

And when they return, it is likewise inevitable that at least some HCPs will follow the instructions on Mylan's Proposed Labels. Dr. Kohler testified credibly to having done so. Tr. 886:11-890:1-6 (Kohler). *see also* PTX-220 at 9 ("The vast majority of patients" were initiated onto Trinza "based on the prescribing guidelines.").

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[13] On Re-direct, Dr. Berger testified that the "20 to 30%" could "include more than nine months" after the prior dose. Tr. 310:12-17. But Dr. Berger did not specify what percentage of that 20 to 30% was outside of the claimed 4 to 9-month window. The Court finds, based on Berger's testimony and other credible testimony, that at least some percentage of PP3M patients would inevitably return between 4 to 9 months after their last missed dose.

[14] Mylan objected to Janssen using Dr. Kohler's testimony to support Janssen's infringement argument when he was called only for secondary considerations, and in light of Janssen's numerous objections to Mylan's infringement questions. Mylan Br. 25, n.11; Mylan Resp. Br. 27; Tr. 909:6-9, 927:19-20, 928:19-24, 929:11-13, 930:21-22, 933:25-934:3 As an initial matter, the Court notes that its direct infringement findings do not hinge solely on Kohler's testimony—there is other evidence in the record, including Dr. Berger's testimony, of inevitable infringement. Moreover, the Court agrees with Janssen that it can correct Mylan's incorrect statement that "Janssen chose to forego any testimony from a prescribing physician who had or would follow the claimed missed-dose regimen." Mylan Br. 25. Having placed the matter at issue by making this false assertion, Mylan cannot prevent Janssen from pointing out that the statement's inaccuracy. And in any event, there is significant "overlap in the proofs required on the issues of validity and infringement." *P&G v. Nabisco Brands, Inc.*, 604 F. Supp. 1485, 1492 (D. Del. 1985).

Dr. Berger testified that he does not use the claimed missed dose dosing instructions because providers should not "blindly follow the prescribing information." Tr. 204:15-23, 231:9-21 (direct); 261:14-19 (cross). But even if this Court were to accept that testimony as credible, he nevertheless conceded that he had supervised medical residents who had "tried to reinitiate" patients on Trinza who had missed a dose between 4 and 9 months ago. Tr. 257:14-25 (supervising residents who consulted Trinza label when their patients missed PP3M 4-9 months ago); Tr. 264:24-265:4 (equating drug label to a speed limit and admitting that he himself follows the speed limit); *see also* Tr. 263:16-19 (Q: [S]ome health care providers do follow label instructions for patients who have missed a dose of PP3M by 4 to 9 months, right? A: I'm sure they try."), 263:22-264:2 (Berger).

The Court simply cannot credit Dr. Berger's testimony that not a single HCP would use the claimed reinitiation dosing regimen. But even if that testimony were credible, the standard is inevitable infringement, not universal infringement. Dr. Berger concedes that at least some have attempted it. In other words, upon a patient's inevitable return between 4 and 9 months after a missed dose, it is inevitable that an HCP would at least attempt the claimed reinitiation regimen.

At least one other Mylan witness confirmed as much. Mylan's Rule 30(b)(6) witness, Director of the North America Portfolio Development Team, testified that she "would assume [Mylan's customers] are going to use [its product] according to the label that's provided." Reed Dep. Tr. 204:12-24. Reed also testified that "[Mylan] would provide the label with the product to [its] customers and . . . they can use it accordingly." Reed Dep. Tr. 204:12-24. Because Mylan's Proposed Labels instruct HCPs to use the Asserted Claims' dosing regimens in an infringing manner, Mylan specifically intends for HCPs to use its Proposed ANDA Products in a way that infringes the Asserted Claims.

The Court is unpersuaded by Mylan's contention that its Proposed Labels discourage infringement by warning that missed doses should be avoided. Mylan Br. 28-29. This is essentially a repackaged version of Mylan's dual-actor divided infringement theory, rejected above, that a patient missing a dose is the Asserted Claims' first step. *See* Mylan Resp. Br. 24 ("[T]he label expressly discourages taking the first step, counseling that patients *should not* miss their doses.") (emphasis in original).

Here, the Proposed Labels discourage missed doses, but do not discourage or make optional the practice of the Asserted Claims (or any claimed steps) in the inevitable situation that doses *are* missed. *See* Tr. 884:4-7 (Kohler) ("[P]eople who go on to [LAIs] for different reasons have been shown to have a high rate of nonadherence. So nonadherence will occur again."); 1060:17 (Berger) (acknowledging that nonadherence is a common occurrence with Trinza); 1092-193 (Mulhern) (summarizing literature on schizophrenia patient/Trinza nonadherence); *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 352 F. Supp. 3d 352, 398 (D.N.J. 2018) ("The *only* way to follow these labels is to administer abiraterone, together with prednisone, in specified doses, to a mCRPC patient."); *cf. Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 547 (D. Del. 2014) (label instructed that the claimed method itself should be avoided); *cf HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) (one of the claimed steps was optional).

Nor is the Court persuaded by Mylan's argument that it does not induce infringement because its infringing instructions are not found in the "Indications and Usage" section of its Proposed Labels. There is no such requirement to prove induced infringement. *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018) ("When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, 'the label must encourage, recommend, or promote infringement.'") (cleaned up);

see also Bayer Schering Pharma AG & Bayer HealthCare Pharm., Inc. v. Lupin, Ltd., 676 F.3d 1316, 1324 (Fed. Cir. 2012) ("[T]he point is that the label, *taken in its entirety*, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof.") (emphasis added).

4. Allegedly noninfringing uses do not defeat infringement

Mylan argues that its Proposed Labels cannot induce infringement because they contain numerous non-infringing instructions for PP3M. The Court disagrees.

There is "no legal or logical basis" for limiting induced infringement liability where a proposed label has substantial noninfringing uses. *See Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017). Where a drug label encourages infringement, a defendant "can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses." *Sanofi*, 875 F.3d at 646 (citing *MGM Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 934 (2005); *see also Vanda*, 887 F.3d at 1133 ("[E]ven if the proposed ANDA product has 'substantial noninfringing uses,' [the ANDA applicant] may still be held liable for induced infringement."); *Eli Lilly*, 845 F.3d at 1368-69 ("[A] label that instructed users to follow the instructions in an infringing manner was sufficient . . . even though the product in question had substantial noninfringing uses."). Based on the Court's finding that Mylan's Proposed Labels will inevitably lead HCPs to infringe, Mylan induces infringement whether or not the Proposed Labels also contain noninfringing uses.

But Mylan's arguments also fall short as a factual matter. Dr. Berger cited Mylan's Proposed Labels §§ 2.6 and 2.7 as non-infringing alternatives. But as Dr. Berger conceded, these sections involve switching from PP3M to PP1M injectables (2.6) or PP3M to oral paliperidone (2.7). Tr. 214:25-215:5, 276:17-277:1, 281:7-9 (Berger). Neither is directed to patients who last

received PP3M 4 to 9 months ago. *Id.*; PTX-92 at 8; PTX-133 at 8; PTX-162 at 8; *see also* PTX-595 at 17. Thus, while Mylan's generics may, and likely will, have non-infringing uses, there are no alternatives or non-infringing uses of the 4 to 9-month clinical presentation addressed by the Asserted Claims.

Accordingly, the Court finds that Janssen has demonstrated, by a preponderance of the evidence, that Mylan's Proposed Labels will induce infringement of the Asserted Claims.

B. OBVIOUSNESS: Mylan failed to prove through clear and convincing evidence that the asserted claims of the 693 Patent would have been obvious to a persona of ordinary skill in the art ("POSA")

In its defense, Mylan asserts that the Asserted Claims are invalid for obviousness, *i.e.* that the Asserted Claims would have been obvious to a POSA based on available prior art. The Court disagrees.

"A patent for a claimed invention may not be obtained … if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a [POSA] to which the claimed invention pertains." 35 U.S.C. § 103.

A party asserting a patent's obviousness must prove "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019). Obviousness is a question of law based on underlying facts, including: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill; and (4) objective indicia of nonobviousness. S*ee Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

1. The PP3M prior art was likely considered by the PTO Examiner

Having been approved by the Patent Office, the Asserted Claims are generally presumed valid. 35 U.S.C. § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 110-14 (2011). Mylan argues, however, that no deference is owed to the PTO's issuance of a patent because certain PP3M prior art was not before the PTO's claim examiner: JAMA,[15] the 2014 Press Release,[16] and NCT 423.[17] Mylan Br. 49-50. Janssen counters that the challenger's overall burden to demonstrate invalidity by clear and convincing evidence remains unchanged.

Both are correct. Mylan is correct that "if the PTO did not have all material facts before it, its considered judgment may lose significant force." *i4i*, 564 U.S. at 111. But this does not change the challenger's burden; it simply means that the burden "may be easier to sustain." *Id.* Or phrased differently,

> When new evidence touching validity of the patent not considered by the PTO is relied on, the tribunal considering it is not faced with having to disagree with the PTO or with deferring to its judgment or with taking its expertise into account. The evidence may, therefore, carry more weight and go further toward sustaining the attacker's unchanging burden."

Id. (citing *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984)).

That said, a dispute about whether prior art was previously before the examiner may be evaluated by a factfinder in the context of the challenger's overall burden. *i4i*, 564 U.S. at 111. Here, the Court finds that the PTO examiner conducted prior art searches on the East and Google

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[15] Berwaerts et al., *Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia*, Journal of the American Medical Association ("JAMA") Psychiatry 72(8) (2015). PTX-113.

[16] Janssen Investigational Treatment for Schizophrenia Shows Positive Efficacy, Delays Relapse (2014). PTX-160.

[17] ClinicalTrials.gov archive, *History of Changes for Study: NCT01515423, Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Patients With Schizophrenia*. PTX-158.

Scholar databases. DTX-8 at 193. Although the search terms used on Google Scholar were apparently not recorded, the Examiner's search queries on East included "paliperidone," "three month," and the inventor names. *Id.* 205-06, 236-37. It is therefore likely that the Google Scholar search would have included any PP3M prior art. *See,* Tr. 691:2-7 (Forrest) ("assum[ing]" that Google Scholar would include JAMA).[18] However, even if the PTO Examiner did not consider all of the PP3M prior art, Mylan would nevertheless have failed to meet its burden.

2. *Mylan failed to prove that every element of the Asserted Claims was known in the prior art*

"An obviousness determination generally requires a finding that 'all claimed limitations are disclosed in the prior art.'" *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021) (quoting *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014)). But an "invention is not obvious simply because all of the claimed limitations were known in the prior art.'" *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019). Instead, courts ask "whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references." *Id.* (cleaned up). "The presence or absence of a motivation to combine" and what constitutes "a reasonable expectation

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[18] To the extent that Mylan argues that the Court must disregard such evidence, its citation to *Sun Pharma Glob. FZE v. Lupin Ltd.*, No. 18cv02213, 2021 U.S. Dist. LEXIS 42600 (D.N.J. Mar. 8, 2021), is inapposite. In that matter, the Court excluded testimony about an examiner's search history, but did not exclude the fact of the search or the exact query. *Id.* *8-9. Where there is documentary evidence in the record, the Court may consider it. *See Elan Corp., PLC v. Andrx Pharm., Inc.*, No. 98-7164, 2008 U.S. Dist. LEXIS 94525, at *284-85 (S.D. Fla. Aug. 12, 2008) (finding that "the Examiner presumably found the [prior art], determined that it was unimportant to the patentability of the [claimed invention], and chose not to cite it as material prior art."); *cf Comcast Cable Communs., LLC v. Sprint Communs. Co., LP*, 203 F. Supp. 3d 499, 547 (E.D. Pa. 2016) ("Expert testimony about the subjective knowledge or state of mind of the examiner is not admissible *in the absence of any support in the record*.") (emphasis added).

of success" are questions of fact. See *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) (cleaned up).

In assessing obviousness, factfinders "should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). "Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (internal quotation marks omitted).

Here, Mylan has failed to demonstrate that all claimed limitations were disclosed in the prior art, that a skilled artisan would have reason to combine the prior art references, and that the skilled artisan would have a reasonable expectation of success from doing so. The Court agrees with Janssen that Mylan's obviousness case can best be characterized as a "hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (cleaned up). Mylan's expert, Dr. Forrest, cherry-picked from the prior art; when one data point did not lead to the desired conclusion (the Asserted Claims' reinitiation regimen), he chose another that did.[19]

[19] Though the Court details disagreements with Dr. Forrest's specific findings below, other general indicia undermined the persuasiveness of his testimony. Prior to his work in this case, Dr. Forrest had: never seen the 693 Patent, never worked with antipsychotics, no experience with treating psychotic disorders, never done any work that involved direct patient care, and no experience with paliperidone. Tr. 676:20-677:11 (Forrest). Mylan's counsel provided copies of the references and the specific combinations that he relied on to support obviousness. Tr. 678:14-25 (Forrest). Dr. Forrest was retained in February 2022. Tr. 679:5-9 (Forrest). On March 9, 2022, weeks after being retained, Dr. Forrest signed a 189-page expert report that included a technical tutorial of PP; a description of the 693 Patent; an explanation of the 693 Patent's prosecution history; a summary of 15-16 separate references; and a detailed basis for his invalidity opinions on obviousness, non-

Neither the PP3M references (JAMA, the 2014 Press Release, and NCT 423) nor the PP1M references (Invega Sustenna Label, the 536 Publication, the 519 Publication, and Samtani 2009) disclose or suggest the Asserted Claims' limitations. Mylan failed to prove that every element of the Asserted Claims was known in the prior art because, as a whole, they assert a unique combination of elements: (1) a missed dose regimen for PP3M; (2) administered to a specific patient population whose last dose of PP3M was 4 to 9 months ago; (3) treating a patient who had been advanced from PP1M to PP3M with PP1M reinitiation loading doses; and (4) returning the patient to PP3M treatment without first stabilizing the patient on PP1M for several months. Tr. 538:2-20 (Sommi).

As an initial matter, an exception to the general rule requiring a challenger to identify *all* claim limitations in the prior art is where the POSA's "common knowledge" may supply a *missing* limitation. *See Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361-62 (Fed. Cir. 2016). But that exception applies only where "the limitation in question [is] unusually simple and the technology particularly straightforward." *Id.* at 1362; *accord Koninklijke Philips NV v. Google LLC*, 948 F.3d 1330, 1338 (Fed. Cir. 2020). And even then, "'common sense'…cannot be used as a wholesale substitute for reasoned analysis and evidentiary support." *Arendi*, 832 F.3d at 1362 (concluding that Board erred in relying on "common sense" based on "conclusory statements and unspecific expert testimony"); *Koninklijke*, 948 F.3d at 1338.

To the extent that Mylan argues that a POSA could have used "common sense" to arrive at the Asserted Claims' reinitiation regiment, Dr. Forrest relied entirely upon the prior art without

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enablement, lack of written description and indefiniteness. Tr. 679:5-680:2 (Forrest). In that time, he also "developed a PK model and ran simulations." Tr. 679:22-680:2 (Forrest). Just a few weeks later, on March 31, 2022, Dr. Forrest submitted another expert report on invalidity of two separate patents in a different patent litigation on a different drug involving a completely different disease, *i.e.*, heart failure. Tr. 680:8-681:12 (Forrest).

mention of "common sense." *See, e.g.*, Tr. 474:7-475:15 (Forrest); Forrest Demonstratives Slide 6 ("The prior art renders obvious the asserted claims of the '693 patent[.]"); *id.* at Slide 43 ("The Approach to Missed Doses for PP3M Was Taught by the Prior Art."). "Common sense" or "common knowledge" were not mentioned at trial. To the extent that Dr. Forrest's testimony regarding "routine optimization" is meant to represent a POSA's "common sense," his testimony was too vague to supply missing claim limitations.

But even if the testimony regarding "common sense" had been more robust, "common sense" cannot be used to lead a POSA to develop missing elements of the claim because the missing elements are not "unusually simple" or the technology at issue "particularly straightforward." Tr. 555:16-22 (Sommi) (PP1M pharmacokinetics "were rather complicated and complex and very different from what we had up until that point … applying simple math probably wasn't going to work."), 848:15-19 (Gobburu) ("If you change the formulation" from PP1M to PP3M, you "cannot predict the pharmacokinetics of the new formulation."); *see Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("[I]n the medical arts potential solutions are less likely to be genuinely predictable, as compared with other arts such as the mechanical devices in KSR.") (cleaned up). Thus, Mylan has failed to demonstrate obviousness.

Dr. Forrest relied primarily on four PP1M prior art references: the Sustenna label,[20] the 536 Publication,[21] the 519 Publication,[22] and Samtani 2009.[23] None referenced PP3M; rather, the thrust of Dr. Forrest's testimony (and Mylan's obviousness case) is that PP**1**M prior art could be extrapolated to determine the Asserted Claims' PP**3**M reinitiation dosing regimen. For the reasons below, Dr. Forrest's testimony evidenced hindsight-driven reverse engineering, not obviousness. Dr. Forrest cherry-picked PP1M data to arrive at his desired conclusion about PP3M.

a. The Sustenna label

First, Dr. Forrest extrapolated from the Sustenna Label, PTX-106, to estimate the front end of the intermediate window ("[m]ore than 6 weeks to 6 months since last injection") for a PP3M missed dose regimen. PTX-106 at 4-6 (§ 2.3); Tr. 705:2-5 (Forrest). Dr. Forrest noted that the front end of the Sustenna intermediate window started at six weeks, or about 1.4 times the one-month dosing interval of PP1M (30 days). Tr. 707:12-18 (Forrest); Tr. 558:9-10 (Sommi). Dr. Forrest then applied the 1.4x multiplier to PP3M's dosing interval (90 days), and calculated 4.2 months (126 days) as the front end of the intermediate missed dose window for PP3M. Tr. 707:12-18 (Forrest); Tr. 558:9-14 (Sommi). Dr. Forrest concluded that 4.2 months was "approximately" the 4 months recited in the 693 Patent claims. Tr. 707:23-708:2 (Forrest).

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[20] Invega Sustenna Prescribing Information (Rev. 11/2014). PTX-106.

[21] The 536 Publication (US 2011/0105536) is "Dosing Regimen Associated with Long-Acting Injectable Paliperidone Esters." PTX-116 at 1. It taught that simulating missed dose scenarios using PK models could be used to design PP1M missed dose regimens , but does not disclose PP3M dosing regimens. PTX-116 ¶ [0088]; *see also* Figs. 2 and 3; Tr. 435:25-436:2 (Forrest).

[22] A patent application publication of US 2009/0163519, "Dosing Regimen Associated with Long-Acting Injectable Paliperidone Esters," relating to PP1M PTX-115 at 1;Tr. 414:16-21 (Forrest).

[23] Samtani et al., *Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic*, Clin. Pharmacokinet 48(9) (2009): 585-600. PTX-118.

The problem with Dr. Forrest's approach is its inconsistency: when the same extrapolation arrived at different results, he simply ignored them. As Dr. Forrest admitted, if the same logic used on the front end were applied to the back end, a POSA would—at least initially—arrive at 18 months on the back end of the window. Tr. 710:13-25 (Forrest); Tr. 558:20-559:7 (Sommi) (back end of PP1M intermediate window is 6 months, or 6 times the monthly dosing interval; multiplying the PP3M dosing interval by 6 is 18 months). In other words, the same theory would set the back of the PP3M intermediate window at 18 months, "about twice as long" as the 9-month back end recited in the Asserted Claims. Tr. 559:10-13 (Sommi). And the data would refute the theory.

Dr. Forrest's credibility was undermined by his evasive responses on cross-examination when confronted with this inconsistency. Tr. 709:16-711:20 (Forrest) ("Q. Well, applying your own logic then, you would calculate the back end of the intermediate window for PP3M to be 18 months, right?" A. …Let me say no, that I would need to explain further."; "Q. At your deposition, … I asked you the question, 'And if you applied it to the back end, you would get to about 18 months, or about 540 days.' You said yeah. You're replying that, of course, as I discussed in my report, would see there it would be potentially that long. Right? A. Yes."). The Court is persuaded by the testimony of Drs. Sommi and Gobburu, who both explained that a POSA would not have relied on simple extrapolation of PP1M data to arrive at conclusions about PP3M pharmacokinetics, or applied the extrapolation so inconsistently. *See* Tr. 558:15-560:1 (Sommi); Tr. 813:9-12, 814:16-19 (Gobburu).

b. 4-5 Half-Life extrapolation theory

Dr. Forrest posited a different theory based on drug half-life. Tr. 711:22-25 (Forrest). The premise, relying on the 536 Publication, is that it takes about 4-5 half-lives for a drug to be completely eliminated. PTX-116 ¶ [0103]. This, the theory goes, would reveal the back end of

the intermediate window because that is when drug has been essentially eliminated from the patient's blood stream. Tr. 712:2-9 (Forrest); Tr. 560:2-21 (Sommi). The Court is persuaded that a POSA would not have relied on a 4-5 half-life theory, or any theory based on half-life to identify only one end of the window. Tr. 559:19-560:1, 586:18-24 (Sommi). A POSA would have known this assumption to be scientifically unreasonable, and instead "would have used the actual data," *i.e.*, PP3M's actual half-life data. Tr. 560:22-24, 563:11-22 (Sommi), 712:12-14 (Forrest).

However, the half-life of PP3M was not known in the prior art. Tr. 712:25-713:3 (Forrest); Tr. 560:25-561:3 (Sommi). Instead, Dr. Forrest did what a POSA would not have: assumed that PP3M's half-life could be extrapolated from PP3M's dosing interval (every 3 months). Assuming the half-life for PP1M was 30 days (based on its dosing interval), Dr. Forrest multiplied that by three to assume a PP3M half-life of 90 days. Tr. 713:17-20, 717:21-23 (Forrest). That assumption was wrong: PP3M's actual half-life, reported *after* the Patent's filing date, is approximately 120 to 140 days, or 4-4.5 months. PTX-192 at 6; Tr. 817:24-818:6, 861:8-14 (Gobburu); Shaw Dep. Tr. 136:9-12[24] ("[W]ithout measuring the blood levels, you cannot predict what the half-life of Mylan's proposed PP3M is.").

There were other issues with this approach beyond its objective inaccuracy. PP1M's measured half-life was disclosed in the 519 Publication, which taught that PP1M's half-life was "dose-related," Tr. 562:21-25 (Sommi), increasing "from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites." PTX-115 ¶ [0098]; *see* Tr. 713:14-16 (Forrest). In assuming that PP1M's half-life was uniformly 30 days, Dr. Forrest ignored the reported, dose-dependent half-life of PP1M. Tr. 563:1-7 (Sommi).

[24] Dr. Andrew Shaw, Mylan's 30(b)(6) witness.

Dr. Forrest relied on an observation in the 536 Publication that "[t]he results in Table 3 showed that, for all depot antipsychotics, the administration interval was in the range of about 1-2 half-life for each product." PTX-116 ¶ [0103]; Tr. 714:1-5 (Forrest). There are several scientific flaws with this.

First, it ignores that PP1M's actual half-life is not 30 days, but between 25 and 40 to 49 median days depending on dosage. Tr. 717:11-13 (Forrest) (acknowledging as high as 49 days); PTX-115 (519 Publication) ¶ [0098].

Second, even if a POSA were to use the 536 Publication's statement to estimate a half-life for PP1M, it would teach that the 30-day dosing interval for PP1M would be 1-2 half-lives, meaning that 1 half-life would be anywhere from 15 to 30 days for PP1M—again, inconsistent with PP1M's *actual* half-life of 25 to 49 days. Tr. 717:6-13 (Forrest); Tr. 561:9-19 (Sommi).

Third, Dr. Forrest testified on direct that the 536 Publication was "all about paliperidone palmitate." Tr. 430:4-6 (Forrest). But the 536 Publication's half-life observations, set forth in its Table 3, were expressly *not* about PP, but "a literature search [that] was conducted to evaluate the pharmacokinetic characteristics of *other* long acting injectable antipsychotics." PTX-116 ¶ [0102] (emphasis added). The "authors made an observation that there was a relationship between the administration interval and the half-life" for the products listed in Table 3, which did not include PP. Tr. 561:11-14 (Sommi). Confronted with this on cross-examination, Dr. Forrest evaded. *See* Tr. 713:23-715:10 (Forrest).

Utilizing these imperfect data points, Dr. Forrest then multiplied the purported 30-day half-life of PP1M by three and assumed the half-life of PP3M would be about 90 days. Tr. 717:21-23 (Forrest); Tr. 561:9-19 (Sommi). Dr. Forrest then applied his 4-5 half-life theory to calculate the

back end of the intermediate window for PP3M to be at about 12-18 months. Tr. 464:24-465:6 (Forrest); Tr. 564:8-15 (Sommi).

c. Dr. Forrest's JAMA[25] "natural jump" theory

Before trial, Dr. Forrest relied on a PK modeling exercise to identify the back end of the intermediate missed dose window for PP3M as 9 months. Tr. 720:2-6 (Forrest). But at trial, Dr. Forrest unveiled a new theory: that a POSA could have used JAMA to arrive at the 9-month target, and that his PK modeling was only used to validate the conclusion reached under this new theory. Tr. 509:2-4 (Forrest).

Dr. Forrest's JAMA theory relies on the Kaplan-Meier plot of JAMA's Figure 2A, which plots interim data analysis. Then, notwithstanding the author's express conclusion that the plot shows the median relapse time to be 274 days after randomization, *i.e.*, 12 months since the last PP3M injection, a POSA would make a "natural jump" backwards, to 180 days after randomization, *i.e.*, 9 months since the last PP3M injection, as the intermediate window's back end. Tr. 465:14-468:22 (Forrest).

Dr. Forrest's testimony on this was not credible for a few reasons. First, relying on the theory requires exclusive reliance on JAMA's interim analysis to the exclusion of any additional data collected as part of JAMA's final analysis, which evidenced a 395-day (16-month) relapse time after the last PP3M dose. Tr. 703:24-704:4 (Forrest); Tr. 549:9-11 (Sommi); PTX-113 at 4. Dr. Forrest's testimony that "JAMA told us to ignore [the final analysis] data" is not credible based on his own testimony elsewhere that a POSA would "use all the data … at hand." Tr. 720:1; Tr. 720:10-12 (Forrest) ("You would put the appropriate weight on each one and understand which is

[25] Berwaerts et al., *Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia*, Journal of the American Medical Association ("JAMA") Psychiatry 72(8) (2015). PTX-113.

most relevant, but you would use data that is available."). Not once could Dr. Forrest credibly explain why a POSA would use all data in the prior art *except for* JAMA's final analysis. Tr. 720:13-721:13 (Forrest).

That is because a POSA *would* use all data. Tr. 547:17-19 (Sommi). JAMA's interim analysis was conducted because JAMA was a relapse prevention trial involving schizophrenia patients who received placebo; because of "a risk of relapse," interim analysis is conducted for ethical reasons to determine whether to unblind the study early. Tr. 546:4-547:6 (Sommi). But "[w]hen they say the study is over, it may take three, four, five, six months to get all the patients out of the study safely," during which they are "still collecting data." Tr. 547:11-16 (Sommi); PTX-113 at 3 ("Results through the end of the DB phase after early termination of the study (i.e., cumulative data including those from before the interim cutoff data) are reported herein as the final analysis . . . ."). There is no reason, from a POSA's perspective, not to consider all data available.

Second, JAMA's interim (and final) analyses were based on measuring delay of time to relapse, meaning hospitalization or a PANNS score[26] increase. Tr. 543:13-22 (Sommi); Tr. 692:6-11 (Forrest). Neither is a precise pharmacokinetic outcome measuring PP plasma concentration. Tr. 543:23-25 (Sommi). More importantly, Dr. Forrest lacks the expertise to opine on clinical considerations. Tr. 676:23-677:4, 1191:1-2 ("I am not a clinician.") (Forrest). But Dr. Sommi, a Board-certified psychiatric pharmacist with extensive clinical psychiatric experience, testified credibly that a POSA would not have adopted Dr. Forrest's approach of extrapolating the intermediate window for a missed dose regimen from JAMA's relapse data, or at least would have

[26] Positive and Negative Syndrome Scale (PANSS) for Schizophrenia measures the prevalence of positive and negative syndromes in schizophrenia; for example, self-injury, violent behavior, or aggression. Tr. 543:15-22 (Sommi).

incorporated the 395-day relapse datum from the final analysis. Tr. 46:1-50:2, 50:3-51:24, 545:11-546:3, 547:10-11, 548:16-594:14 (Sommi); PTX-113 at 4.

Third, Dr. Forrest never adequately explained the "natural jump." Janssen, however, offers a plausible explanation: the "jump" was simply Dr. Forrest changing his opinion when confronted with an inconsistency. At his deposition, Dr. Forrest testified that JAMA directly taught that the relapse time from randomization[27] was 274 days (9 months), *i.e.*, the Asserted Claims' back end. Tr. 550:18-20. The problem? Dr. Forrest did not factor in that patients had received a PP3M dose 3 months *before* randomization, meaning that—using Dr. Forrest's theory—JAMA actually taught a 12-month back end.

And finally, the JAMA theory also suffers from the same selective-application defect discussed above. Dr. Forrest did not attempt to use JAMA to calculate the front end. Tr. 550:25-551:2 (Sommi). And for good reason; even if JAMA's interim data *could* be used to correctly discern the intermediate window's back end (9 months), using the same method would have revealed a 6-month front end, not the actual 4-month front end borne out by the data and found in the Asserted Claims.

d. Samtani 2009[28]

Dr. Forrest testified that he relied on Samtani 2009 to build PP1M and PP3M PK models, which he used to run Excel simulations. Tr. 480:1-4, 502:18-23, 722:11-13 (Forrest); Tr. 587:10-13 (Sommi). Samtani 2009 "describes the population pharmacokinetic modeling of PP1M formulation." Tr. 820:20-23 (Gobburu). Samtani 2009 discloses a PP1M model developed

[27] "Randomization" refers to the time that patients were placed into one of two groups: those receiving a placebo and those continuing on PP3M. Tr. 548:16-549:3.

[28] "Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic." PTX-118 at 1; Tr. 843:11-19 (Gobburu).

through a pop-PK analysis, based on, and validated with, nearly 16,000 pharmacokinetics samples from about 1,400 PP1M patients. Tr. 566:21-25 (Sommi); Tr. 724:19-22 (Forrest). Samtani 2009 does *not* mention PP3M, and thus does not report any PP3M data. Tr. 724:16-18 (Forrest), 820:24-25 (Gobburu). This theory, too, attempted to extrapolate PP3M's PK from PP1M data—with the same result.

i. Dr. Forrest selectively utilized just a few parameters influencing PK

A POSA would not have built a PP3M PK model using PP1M data gleaned from Samtani 2009, nor would they have used the model to simulate dosing scenarios for PP3M. Tr. 573:11-18 (Sommi); Tr. 813:10-12, 814:16-815:1 (Gobburu). But even if a POSA had attempted that, Samtani 2009 taught that "antipsychotics are rife with inter-patient and intra-patient variability, so the pop-PK takes lots of different factors into account." Tr. 567:21-25 (Sommi). Table III in Samtani 2009 identified 25 such parameters. Tr. 725:2-6 (Forrest); Tr. 821:6-11 (Gobburu).

Among those parameters, Samtani 2009 concluded that the PP's PK is mostly influenced by BMI (body mass index), CLCR (creatinine clearance), INJS (injection site), IVOL (injection volume), and NDLL (needle length). Tr. 568:9-22 (Sommi), 725:7-14 (Forrest); PTX-118 at 1. These parameters, and others, explain the "variability between patients" in how they respond to PP. Tr. 822:3-11 (Gobburu); PTX-145 at 491 ("Substantial differences in response to drugs commonly exist among patients.").

But Dr. Forrest used only 4 of 25 parameters: CL (clearance), Vd (volume of distribution), Ka shift factor for deltoid injection, and the Ka (absorption rate constant). Tr. 725:15-25 (Forrest); Tr. 569:10-15 (Sommi). Dr. Forrest ignored "the variability between patients" where "the range of the blood levels . . . is dictated by whether the patient is a female or is a male . . . [or] is obese or nonobese." Tr. 822:3-11 (Gobburu). Dr. Forrest agrees that a POSA would have understood

this variability. Tr. 724:23-725:1 (Forrest). But a POSA would not have extrapolated PP1M PK data to PP3M, and if attempting to do so, a POSA would have utilized *every* parameter known to influence PP1M PK. Tr. 813:13-16, 821:20-822:11 (Gobburu); *cf* Tr. 720:1 (Forrest) ("You use all the data you had at hand."). Dr. Forrest did not. Tr. 567:12-15 (Sommi), 820:8-10 (Gobburu).

ii. Dr. Forrest's model ignored PP1M's complex absorption

Samtani 2009 teaches that "a dual absorption pharmacokinetic model best described the complex pharmacokinetics of [PP1M]." PTX-118 at 1; Tr. 570:9-12 (Sommi). This reflects PP1M's "biphasic" absorption. Tr. 727:19-21 (Forrest); Tr. 570:9-16 (Sommi). The dual absorption model "is rather more complex than the simplified [model] that was used by Dr. Forrest." Tr. 821:20-822:2 (Gobburu).

Dr. Forrest acknowledges that a biphasic absorption process has an initial zero-order component, Tr. 727:22-24 (Forrest), through which "a fraction of the dose f_2 is absorbed relatively quickly." PTX-118 at 1; Tr. 728:4-6 (Forrest). "[T]he zero order process really talks about where the concentration goes up really quickly. That's a burst of concentration." Tr. 570:17-22 (Sommi). Following the zero-order process, there is a first-order process that "allows that drug to be given over a longer period of time." Tr. 570:23-571:6 (Sommi).

Forrest admitted that PP3M's absorption, like PP1M's, "could also be divided biphasically."[29] Tr. 728:10-13 (Forrest). But Dr. Forrest's models focused only on the elimination phase, using only a simple first-order equation for both PP1M and PP3M. Tr. 728:14-729:7, 742:23-24; Tr. 784:16-19 (Forrest) ("I wasn't trying to count from the very beginning because that's not very important for re-dosing"); Tr. 571:13-19 (Sommi). According to Dr. Forrest, he

[29] Biphasic/dual absorption comprises zero order kinetics, the "burst of concentration" that "goes up really quickly" after injection, and first order kinetics, the "really … slow absorption that accounts for why [PP1M or PP3M] could be given every one or three months." Tr. 570:14-571:6.

did not include a zero-order absorption "because that was such a minor component." Tr. 514:19-21, 729:3-10 (Forrest) ("Yes, 17%"). But, as Dr. Sommi credibly explained, a POSA would have understood that 17% of the drug being absorbed through the zero-order initial burst was not "minor," but "about somewhere between the fifth and the sixth of the dose, … a pretty significant amount." Tr. 571:7-12 (Sommi). A POSA would have found Dr. Forrest's approach "unscientific" because he focuses only on "a sliver of time window and ignor[es] the rest." Tr. 827:11-15 (Gobburu).

iii. Dr. Forrest extrapolates PP3M's absorption rate (Ka) from PP1M

For Dr. Forrest's simple first order model to work, Dr. Forrest needed an absorption rate constant ("Ka") for PP3M. Tr. 735:15-18 (Forrest). But PP3M's Ka was not known in the prior art. Tr. 574:10-14 (Sommi); Tr. 815:2-7 (Gobburu). So, Dr. Forrest extrapolated PP1M's Ka from Samtani 2009's PP1M model and divided it by three. Tr. 735:19-736:5 (Forrest) ("[PP3M] is meant to last three times longer, so one third absorption rate is an estimate."); Tr. 574:15-20 (Sommi); Tr. 815:17-18 (Gobburu).

But Dr. Forrest's extrapolation was not reasonable. Samtani 2009's PP1M Ka was based on a pop-PK model that accounted for biphasic absorption; it could not be plugged into a simple first-order model. Tr. 573:15-22, 574:21-575:1 (Sommi). A POSA would have known that "the pharmacokinetics of PP1M at least were rather complicated and complex and very different from what we had up until that point in the market. …[S]imple math probably wasn't going to work." Tr. 555:16-22 (Sommi).

Dr. Gobburu agreed that this approach was "unscientific." Tr. 802:23-804:7, 813:9-12 (Gobburu) ("The use of [PP1M] data to extrapolate to [PP3M] data is not based on science."). Tr. 813:10-12 (Gobburu). "If you change the formulation" from PP1M to PP3M, you "cannot predict

the pharmacokinetics of the new formulation." Tr. 848:15-19 (Gobburu); Shaw Dep. Tr. at 136:4-8 ("[W]ithout measuring the blood level, you wouldn't know in any way . . . what Mylan's proposed PP3M PK profile would look like."). Thus, a POSA would not have had a reasonable expectation of success in following Dr. Forrest's approach and extrapolating the absorption characteristics of PP3M from data about PP1M. Tr. 815:5-20 (Gobburu); Tr. 555:25-556:4 (Sommi).

But the data undermines that approach's validity. Dr. Forrest posited a simple equation for doing so: "the half-life is related to the natural log of two divided by the Ka." Tr. 489:25-490:1 (Forrest); Forrest Demonstratives Slide 54; *see also* Tr. 576:3 (Sommi) ("So half-life equals 0.693 divided by Ka."). Based on the Ka Dr. Forrest used for modeling a PP3M injection in the gluteal muscle (0.003904), the half-life of PP3M would be 179 days. Tr. 737:25-738:14, 739:18-22 (Forrest). This is nearly twice as long as the PP3M half-life that he assumed for his 4-5 half-life theory—90 days. Plugging Dr. Forrest's PP1M Ka (0.0117) into the same equation reveals the same issue: a 60-day half-life, twice the 30-day half-life Dr. Forrest assumed in his 4-5 half-life theory, and more than the longest known half-life of PP1M, *i.e.*, 49 days. Tr. 576:3-577:3, 577:4-9, 593:13-19 (Sommi).

Dr. Forrest attempted to explain a distinction between half-life for multi-dose versus single-dose injections. Tr. 738:11-16 (Forrest). But Dr. Gobburu credibly explained that the "half-life of a drug . . . is constant over single to repeated dosing in patients. So the half-life would remain the same for paliperidone absorption." Tr. 818:15-819:14 (Gobburu).

iv. Dr. Forrest's "validation"

To validate their PP1M pop-PK model, Samtani 2009's authors used data from two different clinical studies, "includ[ing] 394 (21.9%) subjects who contributed to 2776 (15%) plasma

samples." PTX-118 at 2. Conversely, Dr. Forrest used a handful of median plasma concentration data points for only one PP1M dose (the 100 mg eq. dose) extracted from Figure 1a of Samtani 2009. Tr. 506:9-22 (Forrest). But as Dr. Gobburu credibly explained, "there is a discordance between when the actual data … rise up to the peak versus when the [projected concentrations] raises up to its peak, and the difference in simple terms between the two is about eight days," or "more than 25%" of the 28-day cycle. Tr. 825:16-826:17 (Gobburu); Gobburu Demonstratives Slide 15.

Dr. Forrest relied on that model to project that plasma concentrations would reach or drop below the therapeutic window minimum (7.5 ng/mL) at 9 months to set the back end of the dosing window (as in the Asserted Claims). Tr. 512:25-513:7 (Forrest); Tr. 584:1-7 (Sommi). But again, Dr. Forrest's data is selective: he picked only the 350 mg eq. dose of PP3M to simulate in his model, not the other three (175, 263, and 525 mg eq.). Tr. 740:13-26 (Forrest).

A POSA would have simulated them all if the doses were known, or at least simulated 525 mg eq., the highest dose. Tr. 580:23-582:12 (Sommi); *see also* PTX-192 at 55 ("[redacted]"); PTX-161 (Samtani 2011), "Dosing and Switching Strategies for Paliperidone Palmitate: Based on Population Pharmacokinetic Modelling and Clinical Data" (teaching that PP1M's highest dose had been used to select PP1M's reinitiation regimen). The reason for this, as a POSA would know, is that "people with the highest dose are going to have the highest leftover concentrations." Tr. 581:5-581:11 (Sommi). "[I]f you don't get it right . . . and you restart [the regimen], they've got too much left, you run the risk of overshooting your target concentration and you get side effects." Tr. 581:12-20 (Sommi).

If Dr. Forrest *had* simulated the highest 525 mg eq. dose, the back end of the dosing window would have been "at some point in time after the nine months." Tr. 581:9-11, 584:8-15 (Sommi). Conversely, if Dr. Forrest had simulated a dose smaller than 350 mg eq., the time to cross the 7.5 ng/mL therapeutic minimum threshold would have been sooner than 9 months. Tr. 584:22-24 (Sommi).

3. *Mylan failed to prove motivation to combine prior art to arrive at the Asserted Claims with a reasonable expectation of success*

a. Mylan did not prove any motivation to treat the 4-9 month missed dose patient population with a reasonable expectation of success

Dr. Forrest attempted to identify the 4-month front end of the dosing window using multipliers extrapolated from the Sustenna Label, and JAMA to arrive at the 9-month back end—neither credibly, as discussed above. A POSA would have had no reasonable expectation of success in extrapolating in this manner, but would have at least analyzed the front and back end in the same way. Tr. 558:15-560:1 (Sommi). Dr. Forrest's inconsistent approaches to the data evidence his hindsight-driven approach; in other words, not an approach a POSA would have used, much less one with a reasonable expectation of success. Indeed, Dr. Forrest admitted that this is tantamount to "guessing." Tr. 709:11-14 (Forrest).

b. Mylan did not prove any motivation to use, or a reasonable expectation of success in combining the elements of the prior art

Even if Mylan could prove that the Asserted Claims were disclosed in the prior art, Mylan has also failed to prove by clear and convincing evidence that a POSA would have had a motivation or reason to combine elements of the prior art to arrive at the Asserted Claims' reinitiation dosing regimen with a reasonable expectation of success. *In re Cyclobenzaprine*, 676 F.3d at 1068-69.

The 693 Patent was the first LAIA that recommended using two different long-acting injectable formulations to manage a missed dose. Tr. 557:14-17 (Sommi). The Sustenna Label

instructs to "resume the same dose [of Sustenna] the patient was previously stabilized on." Tr. 556:19-557:6, 589:18-21 (Sommi); PTX-106 at 5. For PP1M missed doses, patients are reinitiated with PP1M (not a different formulation), Tr. 704:21-705:5 (Forrest), at the same dose that was missed (except for the highest dose), Tr. 705:9-13 (Forrest). There was nothing obvious, in other words, about using a non-PP3M formulation to reinitiate a patient that had been advanced to PP3M. Tr. 555:5-7 (Sommi); Tr. 741:7-12 (Forrest) ("the prior art just teaches giving PP1M, then PP3M").

Indeed, even Dr. Berger—who has 50 years of clinical experience with antipsychotics, Tr. 159:14-23—agrees with Dr. Sommi, testifying that "before []Trinza came out" (*i.e.*, before the effective filing date of the 693 Patent), treating a patient who had missed a PP3M dose with PP1M catch-up doses would have been "a bad idea" that was "unsafe," "unreasonable," and/or "unwise." Tr. 262:9-263:9, 1048:9-22 (Berger).[30]

Dr. Forrest argued that the Asserted Claims' reinitiation regimen was obvious because a POSA would have known that PP1M is "faster acting" and "it was known that a PP1M could be used to load them up with drug pretty rapidly so they would be in steady state range for their repeat injections." Tr. 413:20-414:3; Tr. 741:13-18 (Forrest). But Dr. Forrest was unable to point to any credible evidence that taught that PP1M reaches therapeutic levels any faster than PP3M. Tr. 742:5-11 (Forrest).

[30] Dr. Berger later clarified that he did not mean it was unsafe "in all instances," he nevertheless reiterated that it was "far safer" and "far wiser" to reinitiate nonnadherent patients directly on PP3M rather than by using the dosing regimen of the Asserted Claims. Tr. 1043:5-24 (Berger). In other words, Dr. Berger—who rightly emphasized his 50 years of experience as a psychiatric practitioner—saw no reason to use PP1M after a patient has been advanced to PP3M, and had no reasonable expectation of success in doing so. This merely bolsters Janssen's point that reinitiating patients who missed PP3M doses with PP1M was not obvious.

Dr. Forrest suggested that PP1M is faster-acting because PP3M may include larger particle sizes that are slower to absorb. Tr. 400:25-401:5, 406:19-407:3, 410:9-12 (Forrest). But that "would account for the back end of why you can dose this drug for three months," not what happens at the initial burst. Tr. 594:16-595:7 (Sommi) ("We don't know anything about the initial release."). Indeed, Dr. Forrest's flawed modeling suggests identical PP1M and PP3M absorption. Tr. 592:14-17 (Sommi), 828:15-25 (Gobburu); PTX-100D at 2.

Dr. Forrest admitted as much. Tr. 745:8-746:3, 746:18-25, 748:6-10 (Forrest); PTX-100D at 2. And this was true even though his comparison was skewed to favor faster absorption of PP1M by comparing the projected concentrations following 100 mg eq. of PP1M in the *deltoid* muscle versus 350 mg eq. of PP3M in the *gluteal*. Tr. 596:2-9 (Sommi). But deltoid injections result in a faster initial plasma concentration rise than gluteal injections, facilitating a more rapid attainment of therapeutic concentrations. Tr. 726:25-727:2, 747:15-20 (Forrest); Tr. 596:2-4 (Sommi); Tr. 829:6-8 (Gobburu). Dr. Forrest "could have modeled PP1M deltoid to PP3M deltoid," but did not. Tr. 596:2-9 (Sommi). If he had, the initial concentration rise for PP3M "would have been faster," Tr. 749:10-14 (Forrest), undermining Dr. Forrest's assumption that PP1M is "faster acting." Tr. 829:13-17 (Gobburu).

As Drs. Gobburu and Sommi explained, since the art lacked PK data about PP3M, a POSA would have had no reason to believe that PP1M would reach therapeutic concentrations faster than PP3M when used for reinitiation. Tr. 593:24-594:13 (Sommi); Tr. 827:24-828:10 (Gobburu); Shaw Dep. Tr. 136:9-12. Nothing in the prior art would have motivated a POSA to use PP1M after a patient advanced to PP3M. Tr. 598:11-13, 598:16-17 (Sommi). Nor would there have been any reasonable expectation that PP1M would reach therapeutic levels more rapidly than PP3M. Tr. 593:24-594:9, 598:18-21 (Sommi). Thus, a POSA relying on Dr. Forrest's modeling-based

approach would have had no reason or motivation to reinitiate PP3M patients in an intermediate time window using PP1M, and, if anything, would have dissuaded from using PP1M. *See* Tr. 829:13-22 (Gobburu).

Other prior art bolsters this point. For example, patients missing an injection of Abilify Maintena, a different LAIA, received a Maintena injection supplemented with oral Abilify. Tr. 590:21-591:9 (Sommi); PTX-168 at 3-4. The Risperdal Consta label, another LAIA, likewise instructed administration of a missed Risperdal Consta injection supplemented with oral antipsychotic, and taught using this approach when "there are no data to specifically address reinitiation of treatment." Tr. 591:10-18 (Sommi); PTX-187 at 7.

c. Mylan did not prove any motivation to use, or a reasonable expectation of success in using, PP1M to reinitiate PP3M

There was also no motivation to use PP3M without first stabilizing the patient for four or more months on PP1M. Every PP3M reference relied on by Dr. Forrest required patients to be stabilized on PP1M for at least 4 months before advancing to PP3M. In the placebo-controlled study—as described in JAMA and the 2014 Press Release—all patients were stabilized on PP1M for 17 weeks before advancing to PP3M. Tr. 542:3-9, 553:10-15, 645:18-21 (Sommi). Similarly, in the study that compared PP3M to PP1M—as described in NCT 423—"[e]verybody was given PP1M" for 17 weeks to be stabilized on PP1M before half the patients advanced to PP3M. Tr. 541:11-18 (Sommi).

Thus, if a patient who missed a dose of PP3M were given PP1M, there would have been no reason or motivation to advance them to PP3M without first stabilizing them on PP1M for at least 17 weeks, since that was the only way PP3M was reportedly used in the prior art. *See* Tr. 686:2-14 (Forrest).

4. Objective indicia of the Asserted Claims' nonobviousness

Objective indicia of nonobviousness, or real-world facts related to the invention, also known as "secondary considerations," are "essential safeguards that protect against hindsight bias" in the obviousness analysis. *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1136-37 (Fed. Cir. 2019); *see also WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) ("The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis."). Long-felt but unmet need for the patented technology, the commercial success of a product embodying that technology, and skepticism that the invention will work are all recognized as objective evidence that the claimed inventions are nonobvious. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379-80 (Fed. Cir. 2012) (collecting cases). Where present, these object indicia "weigh in favor of nonobviousness, although the lack of such evidence does not weigh in favor of obviousness." *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1993).

Contrary to Mylan's contention, there is no "burden-shifting framework" involved in the consideration of nonobviousness in district court litigation. *See In re Cyclobenzaprine*, 676 F.3d at 10777. Objective indicia are "part of the whole obviousness analysis, not just an afterthought." *Leo Pharm. Prods. Ltd. v. Rea*, 726 F.3d 1346, 1357-58 (Fed. Cir. 2013). They "must be considered in *every case* where present." *Apple, Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*) (emphasis added).

To support nonobviousness, objective indicia must bear a "nexus" to the Asserted Claims, *i.e.*, the indicia must be "attributable to the inventive characteristics of the discovery as claimed in the patent." *In re Cyclobenzaprine*, 676 F.3d at 1079 n.6. The determination of nexus is "highly fact-dependent and, as such [is] not resolvable by appellate-created categorical rules and

hierarchies as to the relative weight or significance of proffered evidence." *WBIP*, 829 F.3d at 1331.

Here, the real-world evidence confirms that the Asserted Claims would not have been obvious; rather, the Claims helped fulfill a long-felt clinical need and contributed to Trinza's commercial success. The evidence also showed that some HCPs—including Mylan's expert Dr. Berger—were skeptical of the Asserted Claims. Thus, the evidence supports nonobviousness.

a. The Asserted Claims' dosing regimens helped Trinza fulfill the long-felt but unmet need for a longer, second-generation LAI

"The existence of a long-felt but unsolved need that is met by the claimed invention is … objective evidence of non-obviousness." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). "It is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP*, 829 F.3d at 1332. The need for a "safer, less toxic, and more effective" alternative to existing antipsychotic therapies has been specifically recognized as a basis for finding unmet need. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006).

LAIAs were developed to address a persistent challenge of treating schizophrenia, patient non-adherence, by reducing dosing frequency. Tr. 871:24-873:23 (Kohler); 1034:24-1035:6, 1060:17-25 (Berger). Longer dosing intervals increase adherence. Tr. 873:13-23 (Kohler).

But LAIAs have their disadvantages. First, longer dosing intervals elevate the risk of sustained and debilitating side effects, including painful muscle contractions and extreme restlessness. Tr. 872:14-24, 875:9-18 (Kohler). Unlike oral medications, which are metabolized in days, LAIAs remain in the body for weeks or months, causing side effects to linger and sometimes requiring additional treatment or hospitalization. Tr. 875:9-24 (Kohler). Thus, though

proper dosing is always important, dosing long-acting drugs is more important because the side effects of overdosing will take longer to abate.

The second disadvantage of LAIAs is that HCPs must administer them. Tr. 874:15-18 (Kohler). Returning for medication frequently can be challenging for patients who must balance their schizophrenia treatment with the rest of their lives. Tr. 874:16-21 (Kohler). As of 2015, there were four second-generation LAIAs on the market in the U.S., with dosing intervals ranging from two weeks to five weeks. Tr. 874:3-10 (Kohler); PTX-089C at 10. Given these relatively short dosing intervals, there "definitely was a need" at that time for an LAIA with a longer dosing interval. Tr. 874:13-15 (Kohler).

Trinza met that need by offering a three-month dosing interval that was more than twice as long as any LAIA on the market at the time. Tr. 876:5-9 (Kohler). Dr. Kohler testified that Trinza was "very well received" by the field and that the medication "frees" patients to pursue a "more independent functioning" lifestyle. Tr. 876:4, 883:24-884:3 (Kohler). Dr. Berger agreed that Trinza is "a wonderful drug." Tr. 1058:21-24 (Berger).

But it is not Trinza's long-felt but unmet need that matters here, but the Asserted Claims' missed dosing regimen. Trinza, for all its benefits, did not eliminate nonadherence. Tr. 884:4-7 (Kohler); 1060:17-19 (Berger) (nonadherence remains a "common occurrence"). And nonadherence to a 3-month LAIA presents unique challenges: undertreatment leading to relapse or overtreatment leading to debilitating side effects further undermining adherence. Tr. 886:4-10 (Kohler). The balance between relapse and side effects is further complicated by clinicians' "limited knowledge about pharmacokinetics, pharmacodynamics [and] how long the product lasts to exert clinical efficacy." Tr. 889:15-17 (Kohler).

Enter the Asserted Claims' missed dosing regimen, which provides "clear instructions about how to catch a person up to the previously effective treatment regimen" without requiring experimentation by practitioners with limited pharmacological knowledge. Tr. 884:8-10, 886:4 (Kohler). Trinza would not have met the long-felt need for a longer-acting LAI without the patented missed dose instructions; clinicians "would have been very reluctant in transferring stable patients on Invega Sustenna to Invega Trinza." Tr. 889:21-24 (Kohler).

b. The Asserted Claims' dosing regimens have contributed to Trinza's commercial success

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Evidence of commercial success also requires the patentee to establish this nexus between the claimed invention and the commercial success of a product or method. *Datatreasury Corp. v. Wells Fargo & Co.*, No. 2:06-CV-072, 2010 U.S. Dist. LEXIS 150694, at *54 (E.D. Tex. Feb. 26, 2010); *see Alcon Rsch. Ltd. v. Apotex*, Inc., 687 F.3d 1362, 1371 (Fed. Cir. 2012).

The analysis becomes more complex in situations like this one, where there is no question that a product (Trinza) is clearly commercially successful, but the asserted claims are just a portion of the product. *See Ormco.*, 463 F.3d at 1312 (acknowledging that Invisalign clear orthodontic system was commercially successful, but finding that Invisalign's success was not due to the claimed and novel features, but at least in part to unclaimed features like the aesthetic appeal and improved comfort of transparent devices without brackets and wire). "It is not necessary, however, that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence." *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264,

1273 (Fed. Cir. 1991). Rather, nexus is established with evidence that "consumers would be less likely to purchase [a product] without" the feature enabled by the patented invention. *Apple*, 839 F.3d at 1054-56 (though many other features contributed to the iPhone's commercial success and many iPhone owners did not care about it, the slide-to-unlock feature of the iPhone contributed to its commercial success, which was relevant to nonobviousness).

i. Trinza is a commercial success

"Invega Trinza's been a success in the marketplace" by multiple economic metrics. Tr. 1088:17-18 (Mulhern). Trinza has generated more than $2.5 billion in sales since launch. Tr. 1083:16 (Mulhern); Tr. 1160:10-13 (Stec); PTX-089C at 3; PTX-530. Sales have grown substantially, with an annual compound growth rate of [redacted]% since launch, and net sales of $570 million in 2021. Tr. 1083:13-18 (Mulhern); PTX-089C at 3; PTX-530. Mylan does not dispute the math. Tr. 1160:6-9 (Stec).

This success is despite a crowded LAIA market: nine second-generation LAIAs introduced since the early 2000s. Tr. 1084:19-21 (Mulhern). Nevertheless, Trinza has captured the third-highest share of both treatment days and sales among second-generation LAIAs, representing 8.8% of the total treatment days and 12.6% of 2021 LAIA revenue. Tr. 1086:1-3; 1086:21-24 (Mulhern); PTX-089C; PTX-410; PTX-528. Trinza has generated a larger share of revenue than [redacted] PTX-089C at 48; PTX-410. Among PP LAIAs, Trinza accounted for [redacted]% of treatment days for patients eligible to switch from Sustenna in 2021; Janssen is correct that this is particularly notable because Sustenna patients are, by definition, adequately treated and therefore not required to switch to Trinza. Tr. 1088:1-12 (Mulhern); PTX-089C at 25-27, 29-30.

ii. There is a nexus between the Asserted Claims and Trinza's success

Janssen readily admits that the missed dose instructions are not the sole driver of Trinza's commercial success, but argues that the Asserted Claims' missed dosing instructions contribute materially to an HCP's decision to prescribe Trinza because the Claims "enable[] the safe and effective treatment in the event of a missed dose of Invega Trinza." Tr. 889:21-24, 892:11-16 (Kohler); 1096:17-20, 1100:2-8, 1101:5-7, 1091:20-21 (Mulhern).

Given the strong potential for missed doses among psychosis patients, clear instructions for resuming treatment following a missed dose are important to any LAIA's safety and long-term efficacy. Tr. 884:8-13 (Kohler). Without such instructions, a clinician would be left to "experiment" on patients with limited knowledge of the drug's PK necessary to determine the best way to resume treatment. Tr. 886:2-10; 890:10-22, 891:23-892:3 (Kohler); PTX-97 at 17. Indeed, a peer-reviewed paper found that the lack of clear directions for re-initiating after a missed dose contributes to clinicians' reluctance to prescribe certain LAIAs in the first instance. PTX-97 at 17.

Janssen's own marketing materials reinforce the nexus. Tr. 1092:6-9; 1094:9-1096:12 (Mulhern); PTX-449 at 1; PTX-509 at 62, 64, 66-68, 76; PTX-510 at 45, 47, 49-51, 58; PTX-513 at 75. Janssen presents the missed dose instructions prominently in its marketing materials and sales training documents, and has even created a "dose illustrator" website to educate clinicians about the pharmacokinetics of Trinza's dosing instructions—including the Claims' missed dose instructions. Tr. 1095:12-1096:3 (Mulhern); PTX-449.

Further supporting the nexus is that a significant number of patients miss LAIA doses. Tr. 884:4-7 (Kohler); 1060:17-25 (Berger) (nonadherence is a "common occurrence … It is an important challenge."). Thus, HCPs would be very unlikely to switch patients already treated with one PP product (Sustenna) to another using the same active ingredient (Trinza), unless that second

product included clear instructions for how to proceed in the event of a missed dose. Tr. 892:11-23 (Kohler). This further supports that the Asserted Claims "contribute[] to the commercial and clinical acceptability of switching a stable Invega Sustenna patient to Invega Trinza," Tr. 1091:18-24 (Mulhern), and therefore "contribute to the marketplace success of Invega Trinza," Tr. 1096:17-20 (Mulhern).

Moreover, the patient population specifically addressed by the Asserted Claims is economically significant. Tr. 1161:1-10 (Stec). Dr. Berger testified that more than 50% of his patients on Trinza miss a regularly schedule dose, and of those, 20 to 30% return more than four months after their prior dose. Tr. 251:5-14 (Berger). Dr. Kohler testified that 5 of the 70 patients he has treated with Trinza, or 7%, have missed a dose and returned in the four-to-nine-month window to resume treatment with Trinza according to the Asserted Claims. Tr. 888:17-21 (Kohler). Both experts' experiences are consistent with the literature on the frequency of missed doses. Tr. 1092:24-1094:8 (Mulhern) (between 17 and 24% of patients depending on the study).

Moreover, the Court is persuaded by Janssen's argument that the nexus between Trinza's commercial success and the Asserted Claims is not limited to sales of doses administered pursuant to the Asserted Claims' reinitiation dosing regimen. Mylan's expert, Dr. Stec, acknowledged that a claimed invention need not be the primary driver of commercial success. Tr. 1167:18-19 ("[I]t doesn't have to be the sole driver[.]"), 1167:23-1168:3 ("Q: If a patent invention contributes but isn't necessarily the primary driver, is it still relevant? A. It potentially could be, but you do an analysis to determine that."). Here, the regimen adds significant "option value" like an airbag or other safety feature in a vehicle; though it is not certain, or even probable, that the airbag will ever be needed, it is a significant purchase factor for many buyers. *See* Tr. 1100:12-1101:2 (Mulhern). Thus, the Asserted Claims have contributed to Trinza's commercial success.

c. Skepticism of the Asserted Claims' efficacy

Evidence of "[d]oubt or disbelief by skilled artisans regarding the likely success of a combination or solution" provides evidence that the solution is nonobvious. *WBIP*, 829 F.3d at 1335. "Concern" that a claimed invention is "risky" is the type of skepticism that "support[s] a conclusion of nonobviousness." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377-78 (Fed. Cir. 2019).

Clinicians have expressed skepticism that the Asserted Claims' reinitiation regimen would successfully re-initiate patients on Trinza. Initially, in service of his non-infringement testimony, Dr. Berger testified that it was "unsafe" and "unreasonable" and a "bad idea" to follow the Asserted Claims' regimen. Tr. 262:9-263:9 (Berger). But later, Dr. Berger, recalled to discuss objective indicia as part of Mylan's obviousness case, testified that the Asserted Claims were not unsafe "in all instances." Tr. 1043:5-10 (Berger). But Dr. Berger then confirmed again that it is "far safer" or "far wiser" to ignore Trinza's FDA-approved label and instead administer the next dose of PP3M to nonadherent patients who return within 4 to 9 months. Tr. 1043:11-24 (Berger).

Dr. Berger also recalled that he and his colleagues doubted whether Trinza would provide the promised therapeutic benefit for the full 3-month dosing interval. Tr. 1058:15-19 (Berger). Dr. Kohler likewise testified that clinicians doubted Trinza's long dosing interval, and that the Asserted Claims' re-initiation regimen could create a "particular challenge," due to its requirement that patients return to their HCP three times in 35 days. Tr. 885:14-18, 889:13-18 (Kohler). Accordingly, there is ample record in the evidence to support Janssen's contention that the Asserted Claims were met with skepticism.

C. INVALIDITY: Mylan failed to establish that the Asserted Claims are invalid

Mylan's invalidity challenge requires it to prove "by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (citation omitted). Dr. Forrest opined, in the alternative to his obviousness arguments, that the terms "PP1M" and "PP3M" appearing in the Asserted Claims are: not enabled and lack written description under 35 U.S.C. § 112. In other words, "[i]f the claims aren't obvious, then [they] are invalid because they lack enablement" and "[t]hose same claims are, if not obvious, invalid because they lack sufficient written description." Tr. 516:1-8, 750:17-751:2 (Forrest). The Court finds these opinions unpersuasive.

1. The Asserted Claims are enabled

"Whether undue experimentation is required is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations [*i.e.*, the *Wands* factors]." *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (cleaned up); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The *Wands* factors include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Cephalon, 707 F.3d at 1336 (quoting *Wands*, 858 F.2d at 737).

The issue with using Dr. Forrest for both obviousness *and* non-enablement/written description is that Dr. Forrest, by virtue of arguing primarily for obviousness (and focusing most

analysis there), lacked "conviction" about the alternative arguments.[31] The arguments are inherently contradictory.

But setting that aside, Mylan argues that a POSA could not practice the full scope of the Asserted Claims without "a lot" of experimentation because (1) the Asserted Claims do not specify the particle size or preferred excipients and concentrations for PP1M and PP3M and the terms are therefore very broad, and (2) there are "no working examples" in the 693 Patent. Tr. 516:21-517:11, 518:3-519:2, 754:6-10 (Forrest). Both are incorrect.

a. The specification provides enough information to practice the Asserted Claims

Although the Asserted Claims do not specify the particle size or excipients (and their concentrations) of PP1M and PP3M, the 693 Patent's specification *does* disclose those features, and others. Tr. 962:13- 963:7 (Little); Tr. 517:23-518:8 (Forrest). Indeed, the 693 Patent contains "ample information in the specification about all the structural features" of PP1M and PP3M such that the specification "hand[s] a person of ordinary skill in the art the recipes to make PP3M and PP1M" for use in the Asserted Claims. Tr. 962:21-963:4 (Little).

First, the 693 Patent contains the concentration and ingredients, specifically PP1M and PP3M "recipes" that contain "sufficient information for a POSA to be able to make and use the claimed invention." Tr. 963:5-7, 964:14-965:8, 968:24-969:4 (Little); PTX-1 at 13:49-56, 13:62-14:3.[32] Second, The 693 Patent specification also provides the particle size range for PP3M and PP1M, including preferred particle size ranges. PTX-1 at 9:38-01; Tr. 971:5-22 (Little).

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[31] The Court is unpersuaded by Dr. Forrest's explanation that he did not understand the phrase, "abiding or strong conviction." Tr. 769:1-20.

[32] PP is the "prodrug" referred to in the specification. A POSA would be familiar with the classes of listed excipients, including wetting agents, suspending agents, and buffers. Tr. 965:12-23 (Little). The 693 Patent specification includes both lists of exemplary excipients and of preferred excipients for PP1M and PP3M. Tr. 965:14-966:20, 967:7-13 (Little); *see, e.g.,* PTX-1 at 10:1-30, 13:3-13; 4:33-39; 13:56-61; 14:9-13.

Third, the 693 Patent specification also provides general and specific manufacturing instructions sufficient to enable a POSA to prepare the particles. PTX-1 at 11:14-29; Tr. 978:13-979:9 (Little). This includes the preferred procedure for adding the surface modifier to the premix, including the concentration of the surface modifier, PTX-1 at 11:50-56; the types of mills that can be used as mechanical means to grind down the particles, PTX-1 at 12:1-6; the preferred grinding media, as well as its density and composition, PTX-1 at 12:24-26; the specific order of steps for adding the premix, PTX-1 at 11:59-61; and the processing temperatures, PTX-1 at 12:34-35. *See* Tr. 979:11-980:19 (Little).

Fourth, the 693 Patent also contains "preferred" examples of the formulations with "specific inactive ingredients" and concentrations, down to the "concentration … to put into the syringe." Tr. 967:7-968:1, 969:5-21, 982:21-983:8 (Little); PTX-1 at PTX-1 at 4:33-39, 13:56-62. The 693 Patent also discloses Sustenna as an example of PP1M and Trinza as an example of PP3M. *See* PTX-1 at 4:18-19, 5:23-24, 5:44-46, and 6:63-65 (Sustenna); PTX-1 at 5:42-47 (Trinza). Dr. Forrest is therefore incorrect that there are "no working examples" of PP1M or PP3M.

b. "PP1M" and "PP3M" are not unduly broad

The 693 Patent describes PP1M and PP3M's structural features. Tr. 962:21-963:4 (Little) (describing structural features as recipes for PP1M and PP3M); Tr. 517:1-6 (Forrest) ("you have to go to the specification to understand what a PP1M and what a PP3M encompasses"); *see also* Tr. 518:3-8, 757:4-8 (Forrest). According to Dr. Forrest, however, the terms PP1M and PP3M encompass "well over 10 million possible combinations" because the structural features include "broad" particle size ranges and "long list[s]" of possible excipients. Tr. 518:3-12, 520:3-14 (Forrest).

However, a POSA would not view the 693 Patent's disclosure about PP1M and PP3M as encompassing 10 million individual formulations. Tr. 980:23-981:6 (Little). It is standard to describe individual formulations using ranges for particle sizes or ingredients. *See* Tr. 1030:23-1031:5 (Little). But even if the Asserted Claims did encompass millions of individual formulations, a POSA would "be able to make any one of those formulations … without undue experimentation." Tr. 982:8-14 (Little).

First, formulations typically contain inactive ingredients or excipients that help provide the correct dosage form for the active ingredient, which provides the pharmacological effect. Tr. 959:14-960:4 (Little). Wetting agents, buffers, and suspending agents are all classes of excipients included in PP1M and PP3M formulations. Tr. 965:14-23 (Little). Changing or trying different wetting agents is something that a POSA could do without undue experimentation. Tr. 968:5-20 (Little). A POSA would be familiar with the classes of excipients used in PP1M and PP3M, as they are "taught this in their education and they know from their experience what the[ese] class[es] of excipients are and what they do" as well as the "amount that you would use." Tr. 965:14-21, 966:12-20. (Little). Here, the 693 Patent discloses preferred excipients and concentrations. PTX-1 at 14:9-13; 13:56-62; Tr. 967:16-968:1 (Little).

As to particle size, Dr. Forrest could only explain his characterization of the particle size ranges as "broad" based on a six-fold difference in the PP3M range and 20-fold difference for PP1M range. Tr. 519:3-15 (Forrest). But that range is easily explainable: it is "very hard to make particles that are all just one size because [POSAs] start with bigger particles" and "grind them down" resulting in "a range" of particle sizes. Tr. 420:2-12 (Forrest) Tr. 961:7-15 (Little) (opining that it is "very common to refer to particle size as a range."). It is difficult to recreate the exact same particle size distribution between batches, meaning that "it's very important to report them

in terms of a range of particle sizes." Tr. 972:2-16 (Little). And Dr. Forrest should know: one of his own patents claims particle size ranges with a 10,000-fold difference. Tr. 761:4-8 (Forrest); *see also* Tr. 976:13-16 (Little) [redacted] Jindal Dep. Tr.[33] 42:20-22, 101:20-24, 103:18-104:7.

Dr. Forrest testified repeatedly that the "different particle sizes and all the different excipients" for PP1M and PP3M would require "a lot of different experimentation to test all the possible combinations." Tr. 517:16-22, 518:9-15, 758:24-759:3. But Dr. Forrest did not proffer evidence that any experimentation is necessary to make and use PP1M and PP3M in the Asserted Claims. To the contrary, a specification "gives a recipe to a person of ordinary skill in the art" such that a POSA would know they "have PP1M" and "have PP3M" by following that recipe without the necessity for experimentation. Tr. 981:19-982:5 (Little). It is undisputed that changes to a formulation can affect its properties, *i.e.*, particle size changes can impact pharmacokinetics. Tr. 848:15-19 (Gobburu); Tr. 1024:18-24 (Little); Tr. 973:1-5 (Little). But there is no evidence that there are any changes here that impede enablement.

Most importantly, Mylan failed to show that *any* particular embodiment of PP3M or PP1M is not enabled. *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) (reversing summary judgment of non-enablement because "[w]ithout any specific examples, the district court's reasoning is too abstract [and] too conclusory"). Dr. Forrest was unable to identify any specific formulation or explain why it could not be made. Tr. 756:20-757:19, 758:2-9, 758:10-19, 765:15-19, 766:6-13, 766:14-767:6, 767:7-13 (Forrest).

[33] Mylan Director of R&D Shantanu Jindal.

c. The *Wands* factors support enablement

First, the "amount of direction or guidance presented" and "the presence or absence of working examples" in the 693 Patent support a finding of enablement. *Cephalon*, 707 F.3d at 1336 (quoting *Wands*, 858 F.2d at 737). The "patent's specification need not 'describe how to make and use every possible variant of the claimed invention.'" *McRO*, 959 F.3d at 1100 (quoting *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003)). There is likewise "no requirement that a specification must disclose what is routine and well known in the art." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Here, the 693 Patent provides guides a POSA to make PP1M and PP3M and use them in the Asserted Claims' dosing regimen, including a recipe-like disclosure of ingredients, concentrations, and particle size, as well as detailed manufacturing instructions.

Second, to the extent that Mylan asserts that "PP1M" and "PP3M" are too broad, the "scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Deuel*, 51 F.3d 1552, 1560 (Fed. Cir. 1995) (quoting *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970)). Here, as discussed above, the Asserted Claims are not unduly broad because they are directed to dosing regimens listing specific formulations, amounts, timing, and injection sites. Nor are "PP1M" or "PP3M" themselves unduly broad, because a POSA would understand the 693 Patent to limit PP1M and PP3M formulations to the specific ingredients, concentrations, and particle sizes (or ranges) in the Patent.

Third, Mylan failed to present any evidence about the quantity of experimentation, which is relevant to determining whether experimentation is undue. *Wands*, 858 F.2d at 737. Even if the terms PP1M and PP3M were understood to encompass tens of thousands of formulations, a POSA would be able to use the 693 Patent's specifications, including manufacturing instructions, to make

any one of those formulations without undue experimentation. *See also Cephalon*, 707 F.3d at 1339 ("The mere potential need for clinical work, without more, is not dispositive."); *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1365-66 (Fed. Cir. 2008) ("Even if clinical trials informed the anticonvulsively effective amount, this record does not show that extensive or 'undue' tests would be required to practice the invention.").

And fourth, Dr. Forrest did not testify that the prior art supported *non*-enablement. *Wands*, 858 F.2d at 737. Here his arguments in the alternative simply emphasize the contradiction between testifying, on the one hand, that the prior art makes the Asserted Claims obvious, and on the other, that they are not enabled because they are too vague. Dr. Forrest testified that "a lot was known about [PP]" formulations in the prior art, and that it would have been obvious to make PP1M and PP3M formulations for use in the Asserted Claims' reinitiation regimen. Tr. 411:23-412:10 (Forrest). Dr. Forrest also testified that the effects of particle size were "well understood." Tr. 406:19-407:3, 409:11-410:12 (Forrest). This explicitly contradicts any argument that the prior art supported *non*-enablement.

2. The Asserted Claims do not lack written description

Mylan also failed to satisfy its burden "to establish by clear and convincing evidence that the written description requirement was not met, in light of the presumption of validity." *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003). The test for written description "is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). This "involves 'an objective inquiry into the four corners of the specification from the perspective

of a person of ordinary skill in the art.'" *Immunex Corp. v. Sandoz, Inc.*, 964 F.3d 1049, 1063 (Fed. Cir. 2020) (quoting *Ariad*, 598 F.3d at 1351).

Here, the entirety of Dr. Forrest's written description testimony was that there are "no working examples of a PP3M" and "no structural features of a PP1M or a PP3M," and that the inventors therefore "don't show they possess the entire claimed range." Tr. 522:13-20 (Forrest). He added that the 693 Patent incorporates art, such as the 843 Patent that "describes a PP1M that's five microns that falls right in the range of what they claimed for PP3M." Tr. 522:20-23 (Forrest).

This can be rejected for the reasons discussed above: the 693 Patent specification provides extensive information about the structural features of PP1M and PP3M including ingredients, concentrations, particle size, manufacturing information, examples of PP1M and PP3M, and commercial embodiments. Based on the specification's disclosure, it was "very clear that the inventors possessed what was a PP1M formulation and PP3M formulation" within the meaning of the Asserted Claims. Tr. 985:10-24 (Little).

Accordingly, based on this and the other analysis above, the Court finds that Mylan has not sustained its burden of demonstrating obviousness by clear and convincing evidence.

IV. CONCLUSION

For the reasons above, the Court finds that Janssen has demonstrated by a preponderance of the evidence that Mylan's Proposed Labels will inevitably induce infringement of the 693 Patent. The Court also finds that Mylan has failed to demonstrate by clear and convincing evidence that the Asserted Claims are invalid. Accordingly, the Court will enter judgment in favor of Janssen and against Mylan as to the 693 Patent. The parties shall submit a joint proposed judgment.

An appropriate Order, which will be filed on the public docket, accompanies this Opinion.

May 15, 2023
Date

Evelyn Padin, U.S.D.J.